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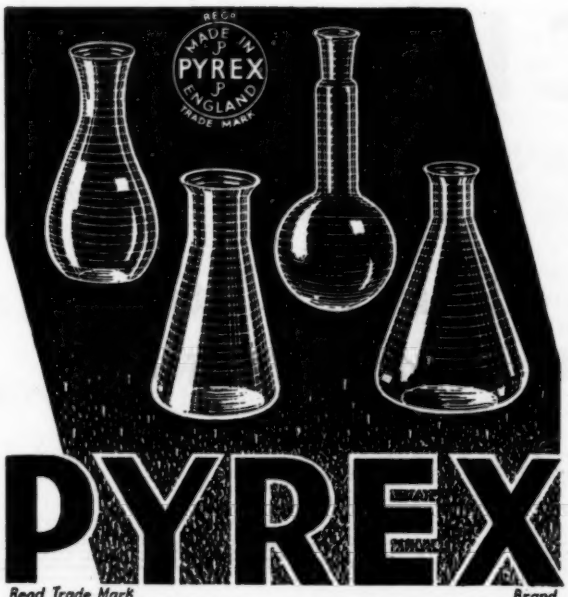

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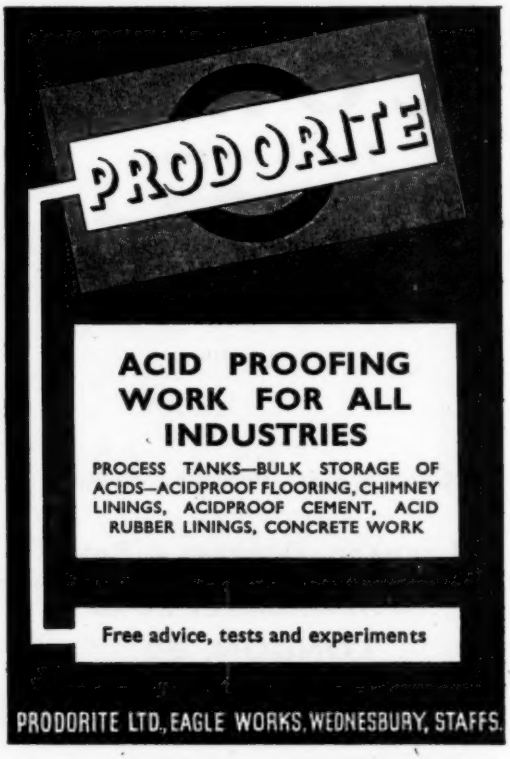
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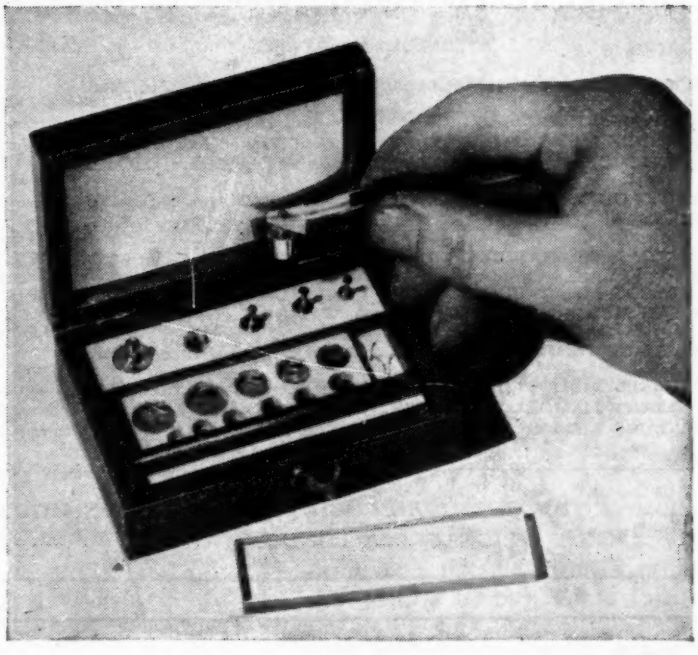

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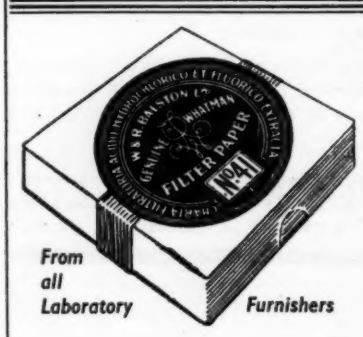

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When the Australian Institute of Tropical Medicine was founded in Townsville, Young was appointed to the post of biochemist and with his wife and daughter—now Dr. Sylvia Young of the Department of Public Health, Jerusalem—spent several happy years in this North Australia setting. In 1919, Professor W. A. Osborne was instrumental in obtaining the appointment of Young as lecturer in biochemistry in Melbourne in succession to the late A. C. H. Rothera. It was then that the writer first met Young and for more than twenty years was closely associated with him in the teaching of biochemistry in the University of Melbourne. He later became Professor of Biochemistry and developed a very sound school in that subject. In all these years Young was an indefatigable worker and ever-delightful associate. He was deeply interested in the applied aspects of biochemistry and conducted researches in the ripening of fruits, especially bananas, and also in the problems associated with the transport of meat. As a member of the National Nutrition Committee and a consultant to the Council for Scientific and Industrial Research he contributed much useful, practical advice.

Young was very fond of walking in the country and for many years was a member of a well-known walking club in Melbourne. His familiar figure was invariably present at the fortnightly outings. He was a charming companion and a welcome visitor everywhere, for he was always interested in the affairs of others and had the extraordinary and most endearing faculty of remembering any trivial happenings in the lives of his very large circle of friends who mourn his untimely passing.

IVAN MAXWELL.

---

15. *The Action of Bases on 1-Diazoanthraquinone-2-sulphonate and its Derivatives.*

By J. I. LYNAS-GRAY and J. L. SIMONSEN.

The action of various bases on 1-diazoanthraquinone-2-sulphonate and on two of its derivatives, having anilino- and bromo-substituents in the 4-position, has been investigated. The mixture of products was separated by chromatographic adsorption, the results being tabulated below.

THE so-called exchange reaction between bases and diazo-compounds (*inter al.*, Griess, *Ber.*, 1886, **19**, 313) was apparently first studied in the anthraquinone series by Wacker (*Ber.*, 1902, **35**, 2593, 3922), who investigated the interaction of what was then regarded as 1-diazoanthraquinone-2-sulphonate with a number of bases. He found that, in nearly all cases, the primary product of the reaction, the diazoaminoanthraquinonesulphonic acid, decomposed with the regeneration of the parent aminoanthraquinonesulphonic acid. As is now known, the acid used by Wacker was the 1-aminoanthraquinone-6-sulphonic acid and not the 2-sulphonic acid. More recently (E.P. 321,217 of 1929) it has been observed that acid wool dyes result from the interaction of bases with 1-diazoanthraquinone-2-sulphonates which are substituted in the 4-position. Although it is recorded that the dyes are not homogeneous, no attempt appears to have been made to elucidate their composition.

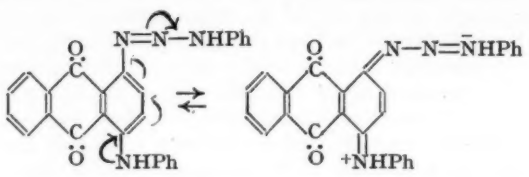
We have now examined the interaction of the diazo-compounds prepared from 1-aminoanthraquinone-2-sulphonic acid (I), 1-amino-4-anilinoanthraquinone-2-sulphonic acid (II) and 4-bromo-1-aminoanthraquinone-2-sulphonic acid (III) with a number of primary aliphatic and aromatic bases under conditions similar to those described in the above-mentioned patent. It was not found possible to separate the products by fractional crystallisation, but resolution was readily effected by chromatographic adsorption of alcoholic solutions of the mixture of sodium salts on alumina. The results are as follows :

Diazo-compound from	Base.	Product.	Yield, %.
(I)	Aniline	(I)	100
(I)	Ammonia	(I)	50
		1-Hydroxyanthraquinone-2-sulphonic acid	50
(II)	Aniline	(II)	15
		1-Anilinoanthraquinone-3-sulphonic acid (IV)	45
		1 : 4-Dianilinoanthraquinone-2-sulphonic acid (V)	40
(II)	*p*-Toluidine	(II)	10
		(IV)	50
		4-Anilino-1-*p*-toluidinoanthraquinone-2-sulphonic acid	40
(II)	*m*-4-Xylidine	(II)	62
		(IV)	32
		4-Anilino-1-*m*-4′-xylidenoanthraquinone-2-sulphonic acid	6
(III)	Aniline	(II)	10
		(III)	20
		(IV)	40
		(V)	30
(III)	Ammonia	1 : 4-Diaminoanthraquinone-2-sulphonic acid	94
		4 : 4′-Diamino-1 : 1′-dianthraquinonyl-3 : 3′-disulphonic acid	5—6
(III)	Methylamine	1-Amino-4-methylaminoanthraquinone-2-sulphonic acid	100

(The yields are calculated upon the reaction product separated, the sulphonic acids being weighed as sodium salts.)

Although the experimental data are insufficient to warrant any theoretical conclusions, it is perhaps permissible to direct attention to the marked effect of a substituent in the 4-position in facilitating the reduction

of the diazo-group or its replacement by NAr. This is due possibly to the formation of the reactive mesomeride (VII) from (VI).

(VI.)  (VII.)

Experimental.

The following general conditions were used in carrying out the reactions summarised above. To a well-stirred suspension of copper bronze (0·003 part) in the base (3 parts) at 0° the diazo-compound, from the appropriate aminoanthraquinonesulphonic acid (1 part), was added during 1 hour (solid bases were used in ethereal solution). After the reaction, which proceeded vigorously with evolution of nitrogen, had moderated, the mixture was heated at 60° for 30 minutes, the excess of base after the addition of aqueous sodium hydroxide removed in steam, the deeply coloured aqueous solution filtered, and the soluble products precipitated by the addition of brine. The mixture of salts was collected, dissolved in alcohol, and purified by chromatographic adsorption on alumina towers.

Aniline and 1-*Diazoanthraquinone*-2-*sulphonate*.—Interaction of aniline with the diazo-compound (9·8 g.) gave a crystalline red salt (10 g.). The chromatogram, after development with alcohol was, apart from a trace of tarry impurity, homogeneous, forming an orange-red zone. This was eluted with water and the substance so obtained crystallised from this solvent in small red prisms identified as sodium 1-aminoanthraquinone-2-sulphonate (Found: N, 4·4; S, 9·8; Na, 7·0. Calc. for $C_{14}H_8O_5NSNa$: N, 4·3; S, 9·8; Na, 7·1%). It gave on bromination 2 : 4-dibromo-1-aminoanthraquinone, crystallising from pyridine in scarlet needles, m. p. 222—223°, both alone and in admixture. On reduction, the sulphonic acid gave 1-aminoanthraquinone, the following conditions being used for this and similar reductions (I.C.I., Lodge, and Tatum, E.P. 322576): The sodium salt of the sulphonic acid (1 g.) and glucose (1 g.) were dissolved in water, and aqueous sodium hydroxide (20%; 2 c.c.) added gradually with stirring at 100°. The base crystallised from benzene in ruby needles, m. p. 243°, both alone and in admixture; the acetyl derivative had m. p. 218°.

In another experiment a suspension of the diazo-compound (10 g.) in water (50 c.c.) was mixed with a solution of aniline in glacial acetic acid (32%; 10 c.c.), the mixture cooled to 0°, and aqueous sodium hydroxide (15%) added with vigorous stirring until the solution was alkaline. The sodium diazoamino-compound (12 g.) was precipitated by the addition of an equal volume of brine, collected, and washed with brine and with benzene to remove tar. The dry salt (10 g.) was dissolved in water (50 c.c.), and sulphuric acid (25%; 250 c.c.) gradually added, the reaction being completed by warming at 50°. Vigorous evolution of nitrogen occurred and the odour of phenol became evident. After completion of the reaction, steam was passed through the solution and phenol was identified in the distillate as tribromophenol, m. p. 95° (0·7 g.). The cooled solution remaining after the steam-distillation deposited a sparingly soluble solid (*A*); this was removed, and the filtrate saturated with salt, which precipitated sodium 1-aminoanthraquinone-2-sulphonate (4 g.), identified as described above. The solid (*A*) (4·5 g.) was extracted with hot water (750 c.c.), which on cooling deposited a crystalline substance (0·3 g.). This separated from acetic acid in copper-coloured leaflets, m. p. 248°, darkening at 238°. Analysis showed this to be the *aniline* salt of 1-diazophenylaminoanthraquinone-2-sulphonic acid (Found: C, 62·3; H, 4·4; N, 11·0. $C_{26}H_{20}O_5N_4S$ requires C, 62·4; H, 4·0; N, 11·2%), the identity being confirmed by comparison with a specimen of the salt prepared from the diazoamino-sulphonic acid.

Ammonia and 1-*Diazoanthraquinone*-2-*sulphonate*.—The diazo-compound (10 g.) was added to aqueous ammonia (100 c.c. containing ammonia, *d* 0·880, 30 c.c.); addition of copper bronze was unnecessary. After the evolution of nitrogen was complete, sodium hydroxide (10%; 50 c.c.) was added, the excess of ammonia boiled off, and an equal volume of brine added to the cooled solution. The reddish-brown sodium salt (10 g.; N, 2·8; Na, 6·9%), which separated, was chromatographed, alcohol developing two zones, the upper being bright red and the lower yellow. The upper zone (2·8 g. from the salt, 6 g.) was sodium 1-aminoanthraquinone-2-sulphonate; from the lower zone a salt (2·7 g.), crystallising in yellow needles, was obtained. This was identified as sodium 1-hydroxyanthraquinone-2-sulphonate, yielding on bromination 2 : 4-dibromo-1-hydroxyanthraquinone, m. p. 232—233° (Found: Br, 42·0. Calc. for $C_{14}H_6O_5Br_2$: Br, 41·9%).

Aniline and 1-*Diazo*-4-*anilinoanthraquinone*-2-*sulphonate*.—The black reaction product (16 g.) from the diazo-compound (10 g.) was chromatographed from an alcoholic solution, the tower on being developed with alcohol giving, in addition to a small zone of tar, three zones: (*A*) rose-violet, (*B*) blue and (*C*) green. The salt (4·5 g.), *sodium* 1-*anilinoanthraquinone*-3-*sulphonate*, from (*A*) crystallised from water in long brownish-red needles with a golden metallic lustre (Found: C, 57·4; H, 2·6; N, 3·2; Na, 5·6. $C_{20}H_{12}O_5NSNa$ requires C, 57·85; * H, 2·9; N, 3·3; Na, 5·5%). The p-*toluidine* salt crystallised from dilute methyl alcohol, in which it dissolved to give a port-wine coloured solution, in purple prismatic needles, decomp. 290°, after sintering at 286—288°, but the temperature of decomposition varied considerably with the rate of heating (Found: C, 66·2; H, 4·6; N, 5·9. $C_{27}H_{22}O_5N_2S$ requires C, 66·7; H, 4·5; N, 5·8%).

The salt (1·5 g.) from (*B*) crystallised from water in light blue needles with a coppery glance and was identified as sodium 1-amino-4-anilinoanthraquinone-2-sulphonate (Found: N, 6·6; S, 7·6; Na, 5·6. Calc. for $C_{20}H_{13}O_5N_2SNa$: N, 6·7; S, 7·7; Na, 5·5%) by the preparation of the p-*toluidine* salt, which crystallised from its royal-blue solution in dilute methyl alcohol in purple prismatic needles, decomp. 269—270°, sintering at 263° (Found: C, 64·9; H, 4·6. $C_{27}H_{23}O_5N_3S$ requires C, 64·7; H, 4·6%). The identity was confirmed by the reduction of the sulphonic acid to 1-amino-4-anilinoanthraquinone, m. p. 203°, both alone and in admixture (Found: N, 8·8. Calc. for $C_{20}H_{14}O_2N_2$: N, 8·9%).

The salt (4·5 g.) from (*C*) crystallised from water in long steel-black needles giving a green aqueous solution. It was identified as *sodium* 1 : 4-*dianilinoanthraquinone*-2-*sulphonate* by analysis (Found: N, 5·9; S, 6·0; Na, 4·5. $C_{26}H_{17}O_5N_2SNa$ requires N, 5·7; S, 6·5; Na, 4·7%) and by reduction to 1 : 4-dianilinoanthraquinone, blue-black needles from benzene, m. p. 214° (Found: N, 7·2. Calc. for $C_{26}H_{18}O_2N_2$: N, 7·2%). The p-*toluidine* salt of the sulphonic acid crystallised from dilute acetone in deep purple, almost black, needles, decomp. 252°, the solution in alcohol or acetone being green (Found: C, 68·7; H, 4·3; N, 7·2. $C_{33}H_{27}O_5N_3S$ requires C, 68·6; H, 4·7; N, 7·3%).

p-*Toluidine and* 1-*Diazo*-4-*anilinoanthraquinone*-2-*sulphonate*.—This reaction was carried out with an ethereal solution of the base and the diazo-compound (14 g.). The purple-black aqueous solution was filtered to remove a black solid (*K*; 3 g.) and deposited a black salt (10g.) after the addition of brine. This was dissolved in alcohol and chromatographed, yielding, in addition to a small zone containing tarry impurities, three zones: a red-violet zone (*X*), a blue zone (*Y*) and a green zone (*Z*). Elution of (*X*) with water gave a salt (5 g.) identified as sodium 1-anilinoanthraquinone-3-sulphon-

* Calculated on the assumption that the residue in the boat was sodium carbonate.

ate by the preparation of its *p*-toluidine salt (see above). The blue zone (*Y*) gave a salt (1 g.) recognised as sodium 1-amino-4-anilinoanthraquinone-2-sulphonate by reduction to 1-amino-4-anilinoanthraquinone and by the preparation of its *p*-toluidine salt. From the green zone (*Z*) a salt (2 g.) crystallising from water in bluish-black needles was obtained; this was *sodium* 4-*anilino*-1-p-*toluidinoanthraquinone*-2-*sulphonate* (Found: N, 5·5; S, 6·2; Na, 4·6. $C_{27}H_{19}O_5N_2SNa$ requires N, 5·5; S, 6·3; Na, 4·5%). It was characterised by the preparation of its *p*-toluidine salt, which crystallised from dilute methyl alcohol in short stout prisms, m. p. 231—232°, identical with the salt described below. On reduction with glucose, 1-*anilino*-4-p-*toluidinoanthraquinone* was obtained, crystallising from benzene–alcohol in blue-black needles, m. p. 250° (Found: C, 80·6; H, 5·2; N, 6·9. $C_{27}H_{20}O_2N_2$ requires C, 80·2; H, 4·9; N, 6·9%).

The sparingly soluble substance (*K*) crystallised from its emerald-green solution in dilute methyl alcohol in black prisms, m. p. 231—232°, and was the p-*toluidine* salt of 4-anilino-1-*p*-toluidinoanthraquinone-2-sulphonic acid (Found: C, 67·0; H, 5·0; N, 7·3; S, 5·4. $C_{34}H_{29}O_5N_3S,H_2O$ requires C, 67·0; H, 5·1; N, 6·9; S, 5·9%). On admixture with alkali and distillation in steam, *p*-toluidine was identified in the distillate by the preparation of its acetyl derivative, m. p. 144—145°, both alone and in admixture; the residue after reduction with glucose gave 1-anilino-4-*p*-toluidinoanthraquinone.

m-4-*Xylidine and* 1-*Diazo*-4-*anilinoanthraquinone*-2-*sulphonate*.—Interaction of the diazo-compound (10 g.) with *m*-4-xylidine (purified through its acetyl derivative) (25 g.) in the presence of freshly precipitated copper (0·1 g.) proceeded readily at 0° and the reaction was completed by heating at 70—80° for 0·5 hour. An alcoholic solution of the black salt (10 g.) isolated in the usual manner was chromatographed and gave three zones: a rose-violet zone (*L*), a blue zone (*M*) and a green zone (*N*). The yields varied considerably in different experiments and the values recorded are only very approximate. The zone (*L*) (31%) gave on elution sodium 1-anilinoanthraquinone-3-sulphonate; *p*-toluidine salt, decomp. 290°; the zone (*M*) (62%) gave sodium 1-amino-4-anilinoanthraquinone-2-sulphonate, *p*-toluidine salt, decomp. 270°. Elution of the zone (*N*) gave on evaporation of the water a somewhat gummy *salt* (6%) which after repeated re-towering was ultimately obtained as an almost black powder crystallising from its green aqueous solution in black needles (Found: N, 5·2. $C_{28}H_{21}O_5N_2SNa$ requires N, 5·4%). The p-*toluidine* salt of 4-*anilino*-1-m-4′-*xylidinoanthraquinone*-2-*sulphonate* crystallised from dilute methyl alcohol in black needles, decomp. 250° (Found: C, 68·8; H, 5·2. $C_{35}H_{31}O_5N_3S$ requires C, 69·4; H, 5·1%). On reduction 1-*anilino*-4-m-4′-*xylidinoanthraquinone* was obtained, crystallising from benzene or ligroin (b. p. 100—120°) in deep blue needles, m. p. 232—233° (Found: C, 80·7; H, 5·3. $C_{28}H_{22}O_2N_2$ requires C, 80·4; H, 5·2%).

This substance was prepared also by the digestion of 4-chloro-*m*-xylene (5 g.) with 1-amino-4-anilinoanthraquinone (0·5 g.) in the presence of freshly precipitated copper (0·1 g.) and sodium acetate (0·2 g.) for 3 hours. The reaction mixture was distilled in steam, and the residue digested with hydrochloric acid for 0·5 hour, collected, and recrystallised from benzene, 1-anilino-4-*m*-4′-xylidinoanthraquinone (0·7 g.) being obtained in blue needles, m. p. 232—233°.

Ammonia and 1-*Diazo*-4-*bromoanthraquinone*-2-*sulphonate*.—Aqueous ammonia (*d* 0·880; 10 c.c.) and copper bronze (0·1 g.) were added to a paste of the diazo-compound (10 g.) in water (100 c.c.). The reaction, which was vigorous, was completed by heating at 70—80° for 0·5 hour. After the addition of aqueous sodium hydroxide, the solution was boiled to expel ammonia, and the product precipitated from the filtered solution by the addition of salt. An alcoholic solution of the black powder (8·5 g.) was chromatographed, yielding two zones, a red and a blue. The former on elution with water gave a red powder (5%) crystallising from hot water in red plates with a golden metallic lustre (Found: N, 4·0. $C_{28}H_{14}O_{10}N_2S_2Na_2$ requires N, 4·3%). The p-*toluidine* salt of 4 : 4′-*diamino*-1 : 1′-*dianthraquinonyl*-3 : 3′-*disulphonic acid* crystallised from dilute methyl alcohol in deep red, prismatic needles, m. p. 234—235°. For analysis it was dried at 100°, but it still apparently contained solvent (Found: C, 57·3; H, 4·6; N, 6·4. $C_{42}H_{24}O_{10}N_4S_2,3H_2O$ requires C, 57·8; H, 4·6; N, 6·4%). This disulphonic acid was conveniently prepared by digesting sodium 4-bromo-1-aminoanthraquinone-2-sulphonate (2 g.) in water (100 c.c.) with copper powder (0·1 g.) and a drop of alkali for 3 hours.

On reduction with glucose in the usual manner, 4 : 4′-*diamino*-1 : 1′-*dianthraquinonyl* was obtained, which crystallised from *m*-4-xylidine in small red plates, m. p. 356—358°. This base was very sparingly soluble in the ordinary organic media, but it dissolved readily in acetic–hydrochloric acid (Found: N, 6·3. $C_{28}H_{14}O_4N_2$ requires N, 6·3%). 2 : 2′-*Dibromo*-4 : 4′-*diamino*-1 : 1′-*dianthraquinonyl*, prepared by the action of bromine on the sodium salt of the disulphonic acid, crystallised from nitrobenzene in red plates with a brilliant green iridescence, m. p. 415—416° (Found: N, 4·9; Br, 26·3. $C_{28}H_{14}O_4N_2Br_2$ requires N, 4·6; Br, 26·6%). Both these dianthraquinonyl derivatives dissolved in sulphuric acid to yield colourless solutions, becoming green on the addition of boric acid.

Elution of the blue-violet zone with water gave a black salt (90%), which was purified by conversion into its sparingly soluble, crystalline, scarlet hydrochloride. The hydrochloride, which readily dissociated, was reconverted into the sodium salt by the addition of aqueous sodium hydroxide. *Sodium* 1 : 4-*diaminoanthraquinone*-2-*sulphonate* crystallised from water, in which it was readily soluble, in small, dark violet needles (Found: N, 8·0. $C_{14}H_9O_5N_2SNa$ requires N, 8·2%). On bromination, the salt gave 2 : 4-dibromo-1-aminoanthraquinone, m. p. 221°, and on reduction 1 : 4-diaminoanthraquinone was obtained, crystallising in black needles, m. p. 267—268°, from dilute alcohol (Found: N, 11·9. Calc. for $C_{14}H_{10}O_2N_2$: N, 11·8%) and yielding a diacetyl derivative, m. p. 268°.

Methylamine and 1-*Diazo*-4-*bromoanthraquinone*-2-*sulphonate*.—This reaction, carried out with the diazo-compound (10 g.) and methylamine (10 g.) in water (100 c.c.), gave a violet-blue powder (8 g.) which was homogeneous in the tower. *Sodium* 1-*amino*-4-*methylaminoanthraquinone*-2-*sulphonate* crystallised from water in blue needles (Found: N, 7·6; S, 9·6. $C_{15}H_{11}O_5N_2SNa$ requires N, 7·9; S, 9·6%). Reduction gave 1-amino-4-methylaminoanthraquinone, violet rhombohedra from toluene, m. p. 198° (Found: C, 71·5; H, 4·6; N, 11·5. Calc. for $C_{15}H_{12}O_2N_2$: C, 71·4; H, 4·8; N, 11·1%). The acetyl derivative separated from methyl ethyl ketone in brown leaflets, m. p. 282°. Gattermann (*Annalen*, 1912, **393**, 160) gives m. p. 195° and 278° respectively for the base and its acetyl derivative.

Aniline and 1-*Diazo*-4-*bromoanthraquinone*-2-*sulphonate*.—An alcoholic solution of the mixture of sodium salts (15 g.) from the diazo-compound (16 g.) was chromatographed yielding four zones: (*S*) rose-violet, (*T*) blue, (*U*) red and (*V*) green. From (*S*), sodium 1-anilinoanthraquinone-3-sulphonate (4 g.) was eluted and identified as its *p*-toluidine salt, decomp. 290°; from (*T*), sodium 1-amino-4-anilinoanthraquinone-2-sulphonate (1 g.), *p*-toluidine salt, decomp. 269°; and from (*U*), sodium 4-bromo-1-aminoanthraquinone-2-sulphonate (2 g.) (Found: N, 3·2; Br, 20·1; Na, 5·7. Calc. for $C_{14}H_7O_5NBrSNa$: N, 3·5; Br, 19·8; Na, 5·7%). The p-*toluidine* salt crystallised from alcohol in red leaflets, seen under the microscope to consist of prismatic needles, decomp. 252°, both alone and in admixture (Found: C, 51·4; H, 3·5. $C_{15}H_{17}O_5N_2BrS$ requires C, 51·5; H, 3·5%). The green zone (*V*) gave sodium 1 : 4-dianilinoanthraquinone-2-sulphonate (3 g.); *p*-toluidine salt, decomp. 252°.

One of us (J. I. L.-G.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant. Our thanks are due also to Imperial Chemical Industries (Dyestuffs) Ltd. for grants and materials and to their Research Committee for valuable suggestions.

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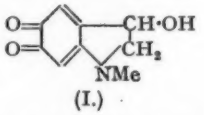
16. *The Oxidation of Adrenaline.*

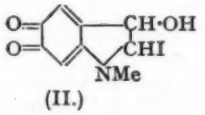
By F. Bergel and A. L. Morrison.

The oxidation of adrenaline and related compounds with oxygen and a catalyst or with potassium iodate has been studied and, in the case of adrenaline, after reductive acetylation, crystalline **5 : 6-*diacetoxy*-1-*methylindole*** has been isolated.

Adrenaline and dihydroxyphenylalanine yield *o*-quinonoid indole derivatives when oxidised by catechol oxidase (Green and Richter, *Biochem. J.*, 1937, **31**, 596) or tyrosinase (Raper, *ibid.*, 1927, **21**, 89) and solutions of similar compounds were obtained in chemical oxidations of adrenaline by Fränkel and Allers (*Biochem. Z.*, 1909, **18**, 401), Kraus (*ibid.*, 1909, **22**, 131), and Green and Richter (*loc. cit.*). The product from the enzymatic oxidation of adrenaline is adrenochrome, probably (I). Richter and Blaschko (J., 1937, 601) obtained the quinone (II) by oxidation of adrenaline with potassium iodate.



(I.)



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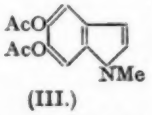


(III.)

In view of the probability that adrenochrome is the precursor of physiologically interesting substances, we some time ago reinvestigated the oxidation of adrenaline and related compounds. We oxidised them either catalytically in presence of palladium–charcoal (as an oxidase model) or repeated Richter and Blaschko's oxidation with potassium iodate.

Further evidence for the correct formulation of the quinone (II) was obtained when it was reductively acetylated with zinc and acetic anhydride and yielded **5 : 6-*diacetoxy*-1-*methylindole*** (III), m. p. 100—101°. Reduction of (II) with sodium hydrosulphite, followed by acetylation, yielded **2-*iodo*-5 : 6-*diacetoxy*-1-*methylindole***, which on reduction with magnesium and acetic acid gave (III) with slightly higher m. p. than previously observed; the mixed m. p., however, showed no depression.

From the red solution obtained by catalytic oxidation of adrenaline when two molecular equivalents of oxygen were absorbed, adrenochrome could not be isolated but a brown melanin-like substance was gradually deposited. When, however, the red solution, before melanin formation, was reduced catalytically or with sodium hydrosulphite, and the resulting pale yellow solution acetylated, a very small amount of a crystalline compound, m. p. 105—110°, was obtained. It did not depress the m. p. of (III) and gave an analysis which fitted fairly well with the theoretical values for (III). We do not regard the identity of this substance with (III) as established, but in present circumstances further work on this subject cannot be undertaken.

No pure substance could be isolated from oxidations of **3 : 4-dihydroxyphenylethylamine** and **3 : 4-dihydroxyphenylalanine**.

Experimental.

***2-Iodo*-5 : 6-*diacetoxy*-1-*methylindole*.**—Adrenaline (2 g.) was dissolved in 2% acetic acid (40 c.c.), and a 4% solution of potassium iodate (80 c.c.) added. After standing for 2 hours at 0°, the iodo-quinone formed was collected, washed with water, suspended in water, and shaken with ether and an excess of sodium hydrosulphite until it had been reduced and passed into solution. The aqueous portion was extracted five times with ether, and the combined extracts washed once with water, dried (sodium sulphate), and concentrated on the water-bath. Pyridine (20 c.c.) and acetic anhydride (60 c.c.) were added and the solution was left overnight at 0° and poured into ice-cold water. The precipitate, dried and recrystallised from methyl alcohol, had m. p. 153—155° (Found: I, 33·9; CH_3·CO, 23·3. $C_{13}H_{13}O_4NI$ requires I, 34·0; CH_3·CO, 23·1%).

5 : 6-*Diacetoxy*-1-*methylindole*.—(A) The iodo-quinone obtained as described above (0·75 g.), anhydrous sodium acetate (2 g.), zinc dust (2 g.), and acetic anhydride (40 c.c.) were refluxed for 1 hour. After cooling, the liquid portion was poured into ice-cold water and after some time this aqueous solution was extracted with ether. The extract was washed free from acid, dried, and concentrated. The residue was partly crystalline and after repeated recrystallisation from light petroleum (b. p. 100—120°) yielded **5 : 6-*diacetoxy*-1-*methylindole***, m. p. 100—101° (Found: C, 63·4; H, 5·2; N, 5·6. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

(B) 2-Iodo-5 : 6-diacetoxy-1-methylindole (0·5 g.) was dissolved in glacial acetic acid (10 c.c.), and magnesium (0·5 g.) gradually added, the temperature rising to about 60°. The mixture was heated on the water-bath until the magnesium had dissolved and was then poured into ice-cold water. The precipitated 5 : 6-diacetoxy-1-methylindole had m. p. 101—103°, not depressed by the specimen prepared in (A).

Catalytic Oxidation of Adrenaline and Reduction of the Product.—Adrenaline (0·5 g.) was suspended in water (50 c.c.), and acetic acid slowly added until the base dissolved and the *p*H was 4—5. 25% Palladium–charcoal (0·5 g.) was suspended in water and shaken with oxygen until absorption ceased. The solution of adrenaline acetate was added, and shaking with oxygen continued, 67 c.c. being absorbed after 3 hours. The dark red solution, on addition of some sodium hydrosulphite, became light yellow. It was cooled with ice and shaken with 4N-sodium hydroxide (10 c.c.) and acetic anhydride (4 c.c.). No solid separated, but ether extracted a small amount of a crystalline material, m. p. 105—110° after recrystallisation from light petroleum (b. p. 100—120°).

Hydrogenation of the deep red solution obtained by the oxidation of 1 g. of adrenaline with palladium as catalyst gave a yellow solution, 75 c.c. of hydrogen being taken up. When the cooled solution was shaken with acetic anhydride (15 c.c.) and 4% sodium hydroxide solution (20 c.c.), a solid separated in small amount, m. p. 105—110° after recrystallisation from light petroleum (b. p. 100—120°).

Mixtures of either of the above products with 5 : 6-diacetoxy-1-methylindole (m. p. 100—101°) melted at 100—110°.

Research Department, Roche Products Ltd., Welwyn Garden City. [*Received, September 5th*, 1942.]

17. 5-*Hydroxyindole.*

By F. Bergel and A. L. Morrison.

5-Hydroxyindole has been synthesised by debenzylation and decarboxylation of *5-benzyloxyindole-2-carboxylic acid*, prepared from 2-nitro-5-hydroxytoluene and the corresponding phenylpyruvic acid.

Although hydroxyindoles are the parent compounds of a number of physiologically important substances, such as bufotenine, physostigmine and harmine, simple 5-hydroxyindoles have not yet been synthesised. For this reason, it also being borne in mind that these or the corresponding indolines may play an important part in adrenaline metabolism, *5-hydroxyindole* has now been prepared by adapting the method used by Blaikie and Perkin (J., 1924, **125**, 296) for the preparation of 5-methoxyindole-2-carboxylic acid to the preparation of the corresponding *5-benzyloxyindole-2-carboxylic acid.*

2-Nitro-5-hydroxytoluene was benzylated in the usual manner to give *2-nitro-5-benzyloxytoluene*, which when condensed with ethyl oxalate in the presence of potassium ethoxide, followed by hydrolysis of the crude product, yielded 2-nitro-5-benzyloxyphenylpyruvic acid. Although not itself obtained analytically pure, the pyruvic acid formed a *phenylhydrazone* which gave correct analytical figures. The crude 2-nitro-5-benzyloxypyruvic acid on reduction with ferrous sulphate and ammonia yielded 5-benzyloxyindole-2-carboxylic acid.

An attempt to decarboxylate this substance not proving very successful, the benzyl group was first removed by catalytic hydrogenation, palladium–charcoal being used, giving *5-hydroxyindole-2-carboxylic acid*, which on decarboxylation by heating with copper powder yielded the desired 5-hydroxyindole. The yields at all stages of this synthesis were very good until the final one, the hydroxyindole being obtained in only 10% yield from the carboxylic acid. The *methyl* ester of 5-hydroxyindole-2-carboxylic acid also was prepared by catalytic hydrogenation of the corresponding benzyloxy-compound.

Experimental.

2-Nitro-5-benzyloxytoluene.—To a solution of sodium ethoxide (sodium, 3 g.; absolute alcohol, 100 c.c.), 2-nitro-5-hydroxytoluene (20 g.) and benzyl chloride (16·6 g.) were added, and the mixture refluxed on the water-bath for 8 hours. The alcohol was then distilled off, and the residue dissolved in ether and washed with water and dilute sodium hydroxide solution. From these aqueous solutions starting material (5 g.) was recovered. The washed ethereal solution yielded 2-nitro-5-benzyloxytoluene, m. p. 70—71° after two recrystallisations from light petroleum (b. p. 60—80°). Yield, 95% (Found: N, 5·8. $C_{14}H_{13}O_3N$ requires N, 5·8%).

2-Nitro-5-benzyloxyphenylpyruvic Acid.—To potassium ethoxide, prepared from potassium (5·3 g.) in ether (150 c.c.) and absolute ethyl alcohol (6·2 g.), freshly distilled ethyl oxalate (19·6 g.) was gradually added, a clear yellow solution being formed. 2-Nitro-5-benzyloxytoluene (32·4 g.), dissolved in ether, was then added, the mixture left at room temperature for 60 hours, 4% sodium hydroxide solution (200 c.c.) added, and the whole shaken vigorously, left for 1 hour, and acidified. The red ethereal solution was repeatedly extracted with 4% sodium hydroxide solution, and the combined extracts washed once with ether, freed from ether, and acidified, 23·4 g. of 2-nitro-5-benzyloxyphenylpyruvic acid being precipitated. Starting material (5 g.) was recovered from the ethereal extracts. The crude acid could not be readily obtained pure by recrystallisation, the m. p. being always very vague (100—105°). The *phenylhydrazone* after recrystallisation from aqueous methyl alcohol had m. p. 152—153° (Found: N, 10·1. $C_{22}H_{19}O_5N_3$ requires N, 10·4%).

5-Benzyloxyindole-2-carboxylic Acid.—The preceding acid (3·8 g.) was dissolved in 24 c.c. of a solution made from 17 c.c. of aqueous ammonia (*d* 0·880), a hot solution of ferrous sulphate (22 g.) in water (24 c.c.) added, and the mixture refluxed and shaken for 1 hour. The iron hydroxide was repeatedly extracted with hot dilute aqueous ammonia; the combined filtrates on acidification gave *5-benzyloxyindole-2-carboxylic acid*, m. p. 193—194° after recrystallisation from dilute acetic acid. Yield, 70% (Found: N, 5·2. $C_{16}H_{13}O_3N$ requires N, 5·2%).

Methyl 5-Benzyloxyindole-2-carboxylate.—(1) The acid (4 g.) was refluxed with 100 c.c. of 6% methyl-alcoholic hydrogen chloride for 4 hours, some of the alcohol distilled off, and water added. The methyl ester, which separated, had m. p. 150—151° after recrystallisation from methyl alcohol.

(2) The ester was also obtained by the action of an ethereal solution of diazomethane on the acid (Found: N, 4·8. $C_{17}H_{15}O_3N$ requires N, 4·9%).

Methyl 5-Hydroxyindole-2-carboxylate.—25% Palladium–charcoal (0·4 g.), suspended in methanol (30 c.c.), was saturated with hydrogen and shaken with methyl 5-benzyloxyindole-2-carboxylate (1 g.) in methanol (100 c.c.) under slight pressure of hydrogen for 6 hours; 90 c.c. of hydrogen were absorbed (calc., 85 c.c.). The methanolic solution was filtered and concentrated; the product had m. p. 146—147° after recrystallisation from benzene. It gave a faint red colour on heating with the Ehrlich reagent, the colour disappearing on cooling. Yield, 80% (Found: N, 7·1. $C_{10}H_9O_3N$ requires N, 7·3%).

5-Hydroxyindole-2-carboxylic Acid.—Palladium–charcoal (0·4 g.), suspended in methyl alcohol (50 c.c.), was saturated with hydrogen and shaken with a solution of 5-benzyloxyindole-2-carboxylic acid (1 g.) in methyl alcohol (100 c.c.) as described above, the theoretical amount of hydrogen being absorbed (90 c.c. in 40 minutes). The solution was filtered and evaporated to dryness in a vacuum, and the residue crystallised from water; it had m. p. 246° (decomp.). Yield, 70% (Found: N, 7·7. $C_9H_7O_3N$ requires N, 7·9%).

5-Hydroxyindole.—5-Hydroxyindole-2-carboxylic acid (0·5 g.) was mixed with copper powder (0·5 g.) and heated at 250° for 10 minutes in an atmosphere of nitrogen. The product was distilled in a high vacuum, heating being carried out in an air-bath. At 200—220° an oil came over which rapidly solidified. When larger quantities than 0·5 g. were used, the yield was poorer. The average yield from five experiments was 0·08 g. After two recrystallisations from benzene–light petroleum (b. p. 60—80°), the pure product was obtained, m. p. 107—109°. Yield, 0·28 g. from 2·5 g. of starting material (Found: C, 72·6; H, 5·2; N, 11·0. C_8H_7ON requires C, 72·2; H, 5·3; N, 10·5%).

Research Department, Roche Products Ltd., Welwyn Garden City. [*Received, September 5th*, 1942.]

18. *Tutin.*

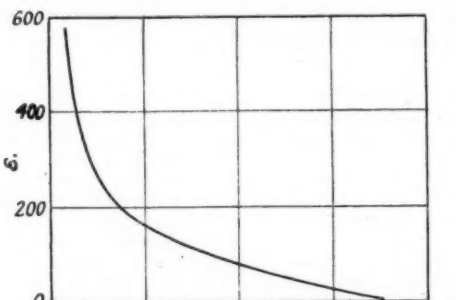
By S. N. Slater.

Tutin, $C_{15}H_{18}O_6$, yields dihydrotutin on hydrogenation and both these substances yield monobromo-substitution products. Parallel reactions have been carried out with picrotoxinin. Tutin gives an *acetyl* derivative.

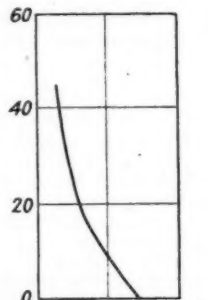
The isolation of the crystalline poison, tutin, from the leaves and seeds of the three species of *Coriaria* found in New Zealand was first reported by Easterfield and Aston (J., 1901, **79**, 120), who described it as a colourless compound, $C_{17}H_{20}O_7$, m. p. 208—209°. It was shown after hydrolysis with dilute mineral acid to reduce Fehling's solution and to give an amorphous precipitate with phenylhydrazine. Methoxy-groups were absent. Concentrated sulphuric acid gave a blood-red coloration with a saturated aqueous solution of tutin and treatment with slaked lime destroyed the poison.

Workers in Japan have since described the isolation of " coriarine " from *Coriaria japonica*, A. Gray. Kinoshita (*J. Chem. Soc. Japan*, 1930, **51**, 99; 1931, **52**, 171) gives the molecular formula $C_{12}H_{14}O_5$, m. p. 212°, and states that a mixed m. p. with tutin which has been further purified shows no depression. On acetylation with acetic anhydride and pyridine an acetyl derivative, m. p. 240°, was obtained. The benzoyl derivative melted at 170·5°. Hydrogenation with platinum in acetic acid yielded hydrotutin, m. p. 240°; acetyl derivative, m. p. 185°; benzoyl derivative, m. p. 182—185°.

Kariyone and Sato (*J. Pharm. Soc. Japan*, 1930, **50**, 659; 1930, **51**, 134) give the m. p. of coriarine as 212—213° and that of tutin from New Zealand sources as 211—212°. The crystalline forms were identical. As a



Tutin in water.



Bromopicrotoxinin in chloroform. (The ε of bromotutin is >1 at 2400A.)

result of analyses the molecular formula $C_{15}H_{18}O_6$ was suggested, which is close to that of coriamyrtin, $C_{15}H_{18}O_5$, and picrotoxinin, $C_{15}H_{16}O_6$, both of which are related pharmacologically to tutin.

Following an improved method of extraction tutin was isolated and purified by recrystallisation from alcohol, the purest specimens melting at 209—210°. Analyses agreed with the molecular formula $C_{15}H_{18}O_6$. The absorption spectrum revealed the absence of any strongly absorbing chromophore within the region examined. Acetylation with acetic anhydride and pyridine gave a *monoacetyl* derivative, m. p. 177°. Hydrogenation of tutin in alcohol with a palladised norit catalyst proceeded smoothly and yielded dihydrotutin, m. p. 190—192°. Dihydrotutin can be brominated just as readily as tutin (see below), yielding *bromohydrotutin*, m. p. 257°, and this ready bromination of the dihydro-derivative has been established also in the case of picrotoxinin. Picrotoxin was hydrogenated in alcohol with a palladised norit catalyst, and the product brominated without further purification, yielding *bromohydropicrotoxinin*, m. p. 255°.

In view of these results it seems doubtful whether the identity of coriarine and tutin has been established. The author has been unable to raise the m. p. of tutin to the figures recorded by Kariyone and Sato and by Kinoshita and there are marked differnces between the m. p.'s of the acetyl and the dihydro-derivatives of the two substances.

Tutin on treatment with bromine water readily forms a monobromo-substitution product (King, unpublished work). A closer investigation of this reaction has shown that two substances are actually produced, which have been designated α- and β-*bromotutin*. The α-form, the main product, melts at 256—257°, and the β-form at 237°. There is thus a marked similarity between this reaction and the bromination of picrotoxinin. The early literature on the bromination of picrotoxinin (Paterno and Oglialoro, *Gazzetta*, 1877, **7**, 193; Schmidt and Lowenhardt, *Ber.*, 1881, **14**, 817; Meyer and Bruger, *Ber.*, 1898, **31**, 2958) is confusing, but Horrmann (*Ber.*, 1912, **45**, 2090) states that the action of bromine on either picrotoxin or picrotoxinin yields a mixture of α- and β-bromopicrotoxinin in which the β-form (needles, decomposing at 280°) predominates. The isolation of this β-form has been confirmed.

As with tutin, the absorption spectra of β-bromopicrotoxinin and α-bromotutin revealed the absence of any strongly absorbing chromophore within the region examined. Of the two halogen derivatives, that from picrotoxinin showed the stronger absorption.

EXPERIMENTAL.

Isolation of Tutin.—The dried leaves and stems of *Coriaria lurida* were boiled for 3 hours with water, and the aqueous liquor concentrated in a continuous flow evaporator. After saturation with sodium chloride and filtration through sand the extract was run in a fine stream through an upwardly moving column of ether (*ca.* 8 feet) in a continuous extraction apparatus designed by Mr. C. G. Martin, M.Sc. The ethereal extract was evaporated to dryness, and the residue dissolved in the minimum quantity of water, neutralised with sodium bicarbonate, and extracted eight times with ether. The dried (sodium sulphate) extracts left on distillation a crystalline product. When this was extracted with ether (Soxhlet), practically pure tutin separated in the boiling flask, m. p. 209—210° after repeated crystallisation from alcohol (Found: C, 61·4; H, 6·2. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%). There was no colour produced with ferric chloride and no reaction with dinitrophenylhydrazine; alkaline permanganate was slowly decolorised and ammoniacal silver nitrate was reduced on heating. When tutin was distilled with zinc dust, extensive charring occurred and only a small quantity of distillate was obtained; this appeared to be phenolic in nature.

Acetyltutin.—Tutin (0·5 g.), acetic anhydride (2·5 c.c.), and pyridine (1 c.c.) were heated at 140° for 1½ hours, the product diluted with water, and the *acetyl* derivative recrystallised from aqueous methyl alcohol; m. p. 177° after shrinking and softening (Found: C, 60·5; H, 6·2. $C_{17}H_{20}O_7$ requires C, 60·7; H, 5·95%).

Dihydrotutin.—Tutin (0·5 g.) in ethyl alcohol was shaken with palladised norit in hydrogen (absorption, 41 c.c.; theo. for 1 double bond, 38 c.c.). After filtration and removal of the solvent the product was crystallised from methyl alcohol, yielding dihydrotutin, m. p. 190—192°, together with small quantities of material of lower m. p.

Bromohydrotutin.—Dihydrotutin (0·33 g.), dissolved in water and treated with excess of bromine water, gave a white *substance* (0·32 g.), m. p. 257° (decomp.), unchanged by recrystallisation from methyl alcohol (Found: C, 48·4; H, 5·1; Br, 21·6. $C_{15}H_{19}O_6Br$ requires C, 48·0; H, 5·1; Br, 21·3%). Mixed with α-bromotutin (see below), it melted at *ca.* 235°.

Bromohydropicrotoxinin.—Picrotoxin (0·5 g.) was shaken with palladised norit in alcohol in hydrogen and when no further contraction took place the catalyst was filtered off and the solvent removed. The residue, dissolved in water, gave with excess of bromine water a white precipitate which, after recrystallisation from alcohol, yielded *bromohydropicrotoxinin* in needles, m. p. 255° (decomp.) after softening (Found: Br, 20·9. $C_{15}H_{17}O_6Br$ requires Br, 21·4%).

Bromination of Tutin.—Tutin (1·0 g.) was dissolved in boiling water, and bromine water added in excess. The material which separated was filtered off and dried (Found: C, 48·7; H, 4·8; Br, 21·4. $C_{15}H_{17}O_6Br$ requires C, 48·3; H, 4·6; Br, 21·4%). Yield, 0·84 g.—fraction I. On standing, the aqueous mother-liquor deposited a further crop of crystalline material (0·12 g.—fraction II). The aqueous mother-liquor was evaporated to small bulk; small nodules were slowly deposited (0·08 g.—fraction III).

Fraction I: M. p. 247° (decomp.). Recrystallisation from methyl alcohol raised the m. p. to 256° (decomp.): *α-bromotutin* (Found: Br, 21·7%).

Fraction II: M. p. 230° (decomp.). Recrystallisation from ethyl alcohol raised the m. p. to 237° (decomp.): *β-bromotutin* (Found: Br, 21·1%).

Fraction III: M. p. *ca.* 230° (decomp.). Recrystallisation from ethyl alcohol raised the m. p. to 257° (decomp.).

Bromopicrotoxinin.—Picrotoxin (0·5 g.) was dissolved in boiling water, and bromine water added. After cooling to room temperature, the precipitate was filtered off and dried—0·29 g., m. p. wide decomposition range up to 259°. After repeated crystallisation from alcohol β-bromopicrotoxinin was obtained in fine needles, m. p. 282° (decomp.).

The expenses of this investigation have been met by a grant from the Hutton Memorial Research Fund of the Royal Society of New Zealand. The author is indebted to Mr. C. L. Carter for microanalyses and to Mr. W. S. Metcalf for spectrographic examinations.

UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, January 26th*, 1942.]

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19. *The Polysaccharides of Carragheen Moss* (Chondrus crispus). *Part I. The Linkage of the* d-*Galactose Residues and the Ethereal Sulphate.*

By J. BUCHANAN, E. E. PERCIVAL, and E. G. V. PERCIVAL.

The results indicate that the galactose residues in carragheen polysaccharides are linked by 1 : 3-linkages as in agar with the ethereal sulphate on C_4.

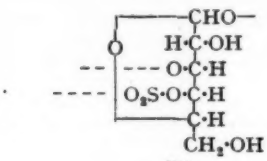
LITTLE progress in the chemistry of carragheen was made until the studies of Haas and his co-workers (*Biochem. J.*, **1921**, **15**, 469, *et al.*). Haas recognised that the polysaccharide (or polysaccharides) was an ethereal sulphate. By extraction with cold water a polysaccharide (C.E.) was obtained which was shown by Russell-Wells (*ibid.*, **1922**, **16**, 469) to contain more sodium and potassium and less calcium than that obtained by extraction with hot water (H.E.), but both products were ethereal sulphates (cf. Butler, *ibid.*, **1934**, **28**, 759).

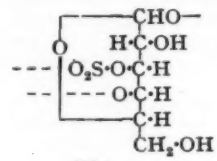
Galactose has long been known to be the main component of the products of hydrolysis and we find that galactose residues constitute at least 31% of the cold, and 33% of the hot extract. Small quantities of glucose have been detected by Müther and Tollens (*Ber.*, **1904**, **37**, 302) and by Haas and Russell-Wells (*Biochem. J.*, **1929**, **23**, 425) in the H.E. We have confirmed this by the isolation of crystalline tetra-acetyl β-methylglucoside and tetramethyl glucopyranose as well as by the isolation of glucosazone, but the quantity of glucose is small. None could be detected in C.E., but the main reason for the difference in physical properties between the two extracts appears to be that H.E. is chiefly a calcium salt, whereas C.E. is a mixture of sodium and potassium salts. Tollens classed carragheen extracts as fructosans ("Handbuch der Kohlenhydrate," 1914, 3rd edition), and colorimetric estimations on galactose-free syrups from hydrolysed H.E. and C.E. indicated that ketoses may be present to the extent of *ca.* 20% in these syrups.

Methylation of C.E. proceeded to OMe, 14·5% and from the hydrolysis products crystalline 2-methyl β-methylgalactoside was isolated. Hydrolysis of a slightly degraded methylated C.E., followed by acetylation and distillation, again yielded a dimethyl galactose triacetate, from which 6-methyl galactosazone was isolated, and a monomethyl galactose tetra-acetate which on suitable treatment yielded an amide which gave a negative Weerman reaction.

Methylation of H.E. (OMe, 14·2%) was followed by hydrolysis, acetylation and fractional distillation of the products. By the isolation of galactosazone from a monomethyl hexose tetra-acetate, and 6-methyl galactosazone from a dimethyl hexose triacetate, complete methylation of both fractions and suitable treatment having given tetramethyl *d*-galactopyranose anilide, it is inferred that 2-methyl and 2 : 6-dimethyl galactose are present in the mixture of hydrolysis products as briefly reported elsewhere (*Nature*, 1940, **145**, 1020).

We believe that the sulphate residue is located on C_4 for the following reasons: The rate of removal of the sulphate by sodium hydroxide solution (4%) at 100° is extremely slow, taking 73 hours to remove 80%. Haas and Russell-Wells (*loc. cit.*) also found that hydrolysis in sodium hydroxide solution (3%) at 110° took 16 hours to proceed to the extent of 20%. This result recalls two earlier examples where alkaline hydrolysis was found to be difficult, 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl α-methylgalactoside (Percival and Percival, J., 1938, 1587) and barium diacetone galactose 6-sulphate, which resisted hydrolysis during 8 hours at 100° with sodium


(I.)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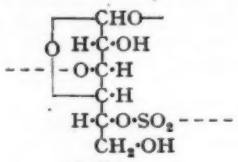
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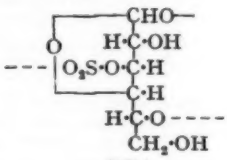
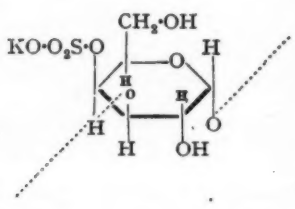

(IV.)

hydroxide solution (8%) (Percival and Soutar, J., 1940, 1475). We have now shown that potassium β-methylgalactoside sulphate, which was proved by Duff and Percival (J., 1941, 830) to yield 3 : 6-anhydro-β-methylgalactoside, is hydrolysed in less than 2 hours under the conditions mentioned for C.E. In all the examples where hydrolysis with alkali is difficult there is no possibility of interaction with another hydroxyl group to form an anhydro-ring, and we therefore suggest that in the carragheen polysaccharides, the sulphate group is placed in such a position that the formation of a 3 : 6-anhydro-ring is impossible. If we accept the evidence from the methylation experiments that the hydroxyl groups on C_2 and C_6 are free in the polysaccharide sulphate, the possibilities may be set out below. (II) and (IV) would hydrolyse with ease to give a 3 : 6-anhydrogalactose residue, and, by analogy with the sugar toluenesulphonates, (III) and (IV) should give ethylene oxide structures. (I), however, can only yield a 2 : 4- or 4 : 6-anhydrogalactose, products which have never been obtained from either sugar sulphates or toluenesulphonates.



The galactose residues of the carragheen polysaccharide may therefore be postulated as joined by positions 1 and 3 (as in agar, galactogen, damson gum and gum arabic) and carrying the sulphuric ester group on C_4. This takes no account of the mode of union of the unidentified portion of the molecule. On account of the positive rotations of both C.E. and H.E. and also their methylated derivatives and the preponderance of *d*-galactose residues it is probable that the units are united by α-linkages.

Experimental.

Preparation of Carragheen Extracts.—The extracts were prepared essentially as described by Haas (*loc. cit.*) from the hand-picked dry weed (300 g.), purchased in bulk from a well-known firm, to yield C.E. (40 g.) and H.E. (90 g.).

Investigation of C.E.—The non-reducing product had $[\alpha]_D^{18°}$ +50° in water (*c*, 0·5). 0·312 G. after prolonged dialysis gave 0·0669 g. of ash as sulphate, *i.e.*, 22·4% (Found: SO_4, 63·8; Ca, 5·5; K, 24·5; Na, 13·7%). C.E. yielded a trace of ammonia on boiling with sodium hydroxide solution (8%) and estimation showed the presence of pentose (1%) [Found: SO_4, 35·1% (by hydrolysis with hydrochloric acid and precipitation in the usual way)].

Hydrolysis. C.E. (2 g.) was treated with sulphuric acid (2·5%, 160 c.c.) at 100° for 5 hours. Treatment in the usual way gave galactosephenylmethylhydrazone (1·03 g.). Galactose (1·006 g.) gave 1·55 g. of galactosephenylmethylhydrazone, so 34% of galactose was present in the dried C.E. C.E. (2·46 g.) was heated at 100° for 20 hours with N/2-oxalic acid. Galactosephenylmethylhydrazone (1·28 g.) was isolated in agreement with the above result. The filtrate was heated with benzaldehyde according to Lüdtke (*Biochem. Z.*, 1929, 419) to yield a syrup, $[\alpha]_D^{17°}$ +9° in water, from which no definite osazone or β-methylglucoside tetra-acetate (see below) could be isolated. Colorimetric estimations indicated the presence of 20—22% of a ketose in this product.

Methylation. C.E. (5 g.) was methylated four times according to Bell (J., 1938, 1461), the product having $[\alpha]_D^{18°}$ +22° in water (*c*, 0·8) (Found: OMe, 14·5; ash, 17·1; SO_4 in ash, 51·6; total SO_4, 24·2%).

Hydrolysis of Methylated C.E.—(i) The above product (3 g.) was hydrolysed with N/2-oxalic acid for 24 hours at 100°, acetylated, and the product (1·15 g.) distilled, b. p. 175—220°/0·02 mm. (Found: OMe, 14·7%).

A portion (0·3 g.) was deacetylated by Zemplen's method, the product (0·17 g.) subjected to two methylations with methyl iodide and silver oxide, the glycosidic methoxyl hydrolysed, and the methylated sugar treated with aniline, giving tetramethyl *d*-galactopyranose anilide, m. p. 196°, not depressed by an authentic specimen.

Isolation of 2-methyl β-methylgalactoside. The acetylated syrup (0·5 g.) was heated according to Munro and Percival (J., 1935, 873), and the product deacetylated with dimethylamine in methanol (20%); removal of acetodimethylamide

at 0·01 mm. gave needles of 2-methyl β-methylgalactoside, m. p. 130°, $[\alpha]_D^{15°}$ +1·5° in water (*c*, 1·0) (Found: C, 45·9; H, 7·7; OMe, 28·9. Calc. for $C_8H_{16}O_6$: C, 46·1; H, 7·75; OMe, 29·8%).

6-*Methyl* β-*methylgalactoside* was prepared from 6-methyl galactose by a similar method, since the identification of the above substance depended mainly on the m. p. recorded by Oldham and Bell (*J. Amer. Chem. Soc.*, 1938, **60**, 324). 6-Methyl β-methylgalactoside had m. p. 114—115°, $[\alpha]_D^{12°}$ ±0° in water (*c*, 0·7) (Found: C, 46·4; H, 7·8; OMe, 28·5. $C_8H_{16}O_6$ requires C, 46·1; H, 7·75; OMe, 29·8%).

(ii) Methylated C.E. (6 g.; OMe, 14·5%) was subjected to a preliminary hydrolysis with N/75-sulphuric acid for 2·5 hours. The product (A) (2·5 g.) was then hydrolysed with N/2-oxalic acid as before, and the reducing syrup transformed into glycosides. The syrup (0·9 g.; OMe, 38·2%) was distilled to yield: (1) 0·33 g., b. p. 160—180°/0·05 mm., $n_D^{16°}$ 1·4700, $[\alpha]_D^{16°}$ +73° in water (*c*, 1·1), OMe 43%; (2) 0·27 g., b. p. 180—220°, $n_D^{16°}$ 1·4807, $[\alpha]_D^{15°}$ +79° in water (*c*, 1·0), OMe 29·5%.

(1) (0·15 g.) was twice methylated with silver oxide and methyl iodide, and the glycosidic methoxyl removed; anilide formation then gave tetramethyl *d*-galactopyranose anilide (0·05 g.), m. p. 196°, not depressed by an authentic specimen. Similarly for (2).

The residue of (1) was treated as before. 2-Methyl β-methylgalactoside was isolated, m. p. 130°, not depressed by previous specimen.

Complete methylation of (2), followed by hydrolysis and anilide formation, gave tetramethyl galactopyranose anilide as before.

A second quantity of (A) was hydrolysed with oxalic acid to yield a syrup (4·5 g.), which was acetylated; the resulting syrup (6·0 g.) was fractionated to give: (1) 0·23 g., b. p. 154—165°/0·05 mm., $n_D^{15°}$ 1·4760; (2) 2·88 g., b. p. 175—185°/0·02 mm.; (3) 2·33 g., b. p. 185—200°/0·02 mm.; (4) 0·52 g., residue.

Fractions (2) and (3) were combined (5·2 g.) and redistilled to give (2*b*) 4·1 g., b. p. 165—176°/0·03 mm., $n_D^{15°}$ 1·4580, OMe 13·0%, and (3*b*) 0·8 g., b. p. 175—200°/0·03 mm., $n_D^{15°}$ 1·4601, OMe 7·9%. Fraction (2*b*) was twice redistilled without improving the separation and was finally acetylated; the product (3·1 g.) on distillation gave (1*e*) 2·35 g., b. p. 180—190°/0·1 mm., $n_D^{16°}$ 1·4580 (Found: OMe, 15·4; $CH_3{\cdot}CO$, 45·2%); (2*e*) 0·5 g., b. p. 195—230°, $n_D^{16°}$ 1·4559.

Investigation of fraction (1e). The fraction (0·974 g.) was deacetylated by Zemplen's method to yield a syrup (0·5 g.), from which (0·16 g.) by suitable treatment an osazone (0·04 g.) was slowly deposited, m. p. 196—198°, not depressed by an authentic but slightly impure specimen of 6-methyl galactosazone (m. p. 195—196°). Another portion of the deacetylated syrup (0·78 g.) gave an osazone in large crystals, m. p. 201—204°, not depressed by a freshly prepared specimen of 6-methyl galactosazone, m. p. 206° (Found: C, 60·0; H, 6·4; OMe, 8·6; N, 15·2. Calc. for $C_{19}H_{24}O_4N_4$: C, 61·3; H, 6·45; OMe, 8·3; N, 15·0%).

Investigation of fraction (3b). The syrup (0·8 g.) was deacetylated and oxidised with bromine as above. A syrupy lactone (0·18 g.) was isolated, $[\alpha]_D^{18°}$ −17° in water (*c*, 2·0) (initial); −15° (4 days, constant). This was converted into the ester and thence into the amide, $[\alpha]_D^{15°}$ +8° (*c*, 0·7), which gave a negative Weerman test, showing C_3 to carry a methoxyl residue.

Hydrolysis of C.E. with N-*Sodium Hydroxide at* 100°.—Dry C.E. (1·771 g.; SO_4, 35·1%) was treated with N-sodium hydroxide (200 c.c.) at 100°, and the amount of sulphate liberated determined at intervals in 10 c.c. portions as barium sulphate:

Time, hrs.	1	10	23	27·7	73
$BaSO_4$, mg.	9	12·5	21·1	22·9	49·8
% Hydrolysis	14·5	20	34	37	80

Hydrolysis of Potassium β-*Methylgalactoside Sulphate with* N-*Sodium Hydroxide*.—Barium β-methylgalactoside sulphate (1·2026 g.) was treated with potassium sulphate (0·2863 g.), the solution made up to N with sodium hydroxide (vol. 100 c.c.), and the sulphate estimated as before: Found: after 1 hour, 27·3 mg. $BaSO_4$, 41·8% hydrolysis; after 2 hours, 65·5 mg. $BaSO_4$, 100% hydrolysis.

Investigation of H.E.—The non-reducing substance after solution in hot water set to a rigid gel on cooling and had $[\alpha]_D^{15°}$ +63° (in water, *c*, 0·3) (ash, 18·7%), not reduced on prolonged dialysis (Found: SO_4, 66·6; Ca, 29·9; K, 2·5; Na, 1·0; SO_4 by fusion with sodium peroxide, 23·8; pentose, 1%).

Hydrolysis. Hydrolysis of H.E. (3·093 g.) with N/2-oxalic acid at 100° for 20 hours and treatment as before gave a syrup (2·46 g.) which yielded galactosephenylmethylhydrazone (1·77 g.) corresponding to 46·4% of galactose in the hydrolysate or 36·9% in H.E. By treatment with benzaldehyde as before the filtrate yielded a syrup (1 g.), $[\alpha]_D^{15°}$ +10° in water (*c*, 1·0). Colorimetric tests indicated the presence of 17% of ketose in this syrup (Found: Pentose, *ca.* 2·4; methyl pentose, *ca.* 1·2%).

Isolation of glucosazone and β-*methylglucoside tetra-acetate.* The galactose-free syrup on suitable treatment gave glucosazone (0·3 g.), m. p. 206—208°, not depressed by an authentic specimen. A syrup obtained in the same way from another experiment (2·5 g.) was acetylated, and the acetate treated according to Munro and Percival (*loc. cit.*); the β-methylglucoside tetra-acetate (0·16 g.) obtained had m. p. 104°, not depressed by an authentic specimen, $[\alpha]_D^{18°}$ −19° in chloroform (*c*, 0·7). The syrup from which this crystallised had $[\alpha]_D^{18°}$ +7° in chloroform and was methylated to yield an oil, $n_D^{13°}$ 1·4495, OMe 60·2%, which on hydrolysis yielded tetramethyl glucopyranose (0·05 g.), m. p. 85°.

Methylation. H.E. (10 g.) was methylated as before to give a glass (7 g.) (Found: OMe, 14·2; ash, 17·7%, containing Ca, 19·9; SO_4, 27·0%).

Hydrolysis of Methylated H.E. and Fractionation.—Hydrolysis of H.E. (7 g.) with oxalic acid gave a syrup (5 g.), OMe 16·8%, $[\alpha]_D^{18°}$ +32° in water (*c*, 0·3). Acetylation gave a syrup (5·6 g.) which yielded: (1) 0·4 g., b. p. 132—140°/0·03 mm., OMe 13·0%; (2) 3·5 g., b. p. 165—180°/0·03 mm., OMe 15·2%; (3) 1 g., b. p. 190—200°/0·03 mm., OMe 9·3%.

Redistillation of fraction (2) gave (2*a*) 2·75 g., b. p. 165—170°/0·03 mm., $n_D^{13°}$ 1·4598 (Found: OMe, 18·5. Calc. for $C_{14}H_{28}O_9$: OMe, 18·6%); (2*b*) 0·5 g., b. p. 185—195°/0·03 mm., OMe 9·6%.

Fraction (3) on complete methylation, hydrolysis, and anilide formation gave tetratmethyl galactopyranose anilide in good yield, m. p. 196°, unchanged on admixture with an authentic specimen. Similarly for (2*a*).

Fraction (3) (0·4 g.) on deacetylation and osazone formation gave an osazone (0·1 g.), m. p. 170—175° (OMe, nil), raised on recrystallisation to 189—191°, not depressed by galactosazone. No mucic acid could be isolated on treating deacetylated (3) with nitric acid under conditions whereby galactose gave a good yield of mucic acid. The galactosazone is therefore formed from 2-methyl galactose.

Isolation of 6-*methyl galactosazone from* (2*a*). Fraction (2*a*) (0·5 g.) was deacetylated and treated with phenylhydrazine and acetic acid. Four crops (0·11 g.; OMe, 7·6%) of osazone were obtained. This osazone on recrystallisation from alcohol had m. p. 201°, not depressed by authentic 6-methyl galactosazone (Found: OMe, 8·0. Calc. for $C_{19}H_{24}O_4N_4$: OMe, 8·3%). This result was twice confirmed.

The slow deposition of this osazone and the properties of (2*a*) are consistent with the presence of 2 : 6-dimethyl galactose triacetate in the latter.

Evidence that C_4 was unoccupied by a methoxyl group was afforded by the fact that glycoside formation on deacetyl-

ated (2*a*) at 16° in 1% methyl-alcoholic hydrogen chloride proceeded with inversion of the sign of rotation. $[\alpha]_D^{13°}$ −27° in 1% methyl-alcoholic hydrogen chloride, equilibrium value.

Thanks are expressed to the Carnegie Trust for the award of a scholarship (to J. B.) and a Teaching Fellowship (to E. G. V. P.) and to Imperial Chemical Industries and the Earl of Moray Endowment for grants.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, September 25th*, 1942.]

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20. *The Polysaccharides of Iceland Moss* (Cetraria Islandica). *Part I. Preliminary Study of the Hemicelluloses.*

By H. GRANICHSTÄDTEN and E. G. V. PERCIVAL.

The investigation is described of a " hemicellulose " extracted from Iceland moss, hydrolysis of which yielded a mixture of sugars containing glucose (89%), galactose (8%) and mannose (3%), and a uronic acid (5%), probably *d*-glucuronic acid. Methylation and fractionation, with molecular-weight determination by the viscosity method, showed that the hemicellulose was not homogeneous, although the mean molecular weight was similar to that of lichenin. Hydrolysis of four fractions (A), (B), (C) and (D), of the methylated hemicellulose resulted in the detection of a terminal end group of *d*-galactopyranose in (A), and end-groups of both galacto- and gluco-pyranose in (B). The main fraction of each hydrolysate consisted of a mixture of trimethyl glucoses and it is thought that the hemicellulose is a mixture of polysaccharides made up chiefly of β-glucose units linked through positions 1 : 2, 1 : 3, 1 : 4 and 1 : 6, the first being a type of linkage not so far reported for glucose units

BUSTON and CHAMBERS (*Biochem. J.*, **1933**, **27**, 1691) have shown that Iceland moss yielded hemicelluloses (3·2%) extractable with cold sodium hydroxide solution (4%), after removal of lichenin (64%) and lichen acids (8·5%). Separation by the copper method of Norris and Preece (*ibid.*, **1930**, **24**, 59) gave two hemicellulose fractions, B_1 and B_2, although the relative yields varied rather widely in different experiments. These fractions were remarkable in containing no glucose in their hydrolysis products, B_1 being made up of galactose (48%), mannose (44%) and uronic acid residues (10·7%), whereas B_2 had galactose (68%), mannose (22%) and uronic acid residues (9%). Our interest in polysaccharides containing galactose led us to study these hemicelluloses to see if there was any similarity in structure to such algal polysaccharides as agar.

Partial separation by precipitation by alcohol from a faintly acid solution of a mixture of hemicelluloses obtained by the method of Buston and Chambers (*loc. cit.*) gave two fractions : (I) (89% of the total) containing uronic anhydride (4·5%); and (II) containing 7·5% of uronic anhydride. The corresponding acetates and methylated derivatives of (I) were shown by fractional precipitation not to be of uniform composition, a fact which serves to emphasise the difficulty of isolating the so-called hemicelluloses in a pure state. On account of this complication and the large quantity of solvents necessary for the extraction of these substances it has only been practicable so far to make a preliminary study of (I).

The uronic acid content is lower than that of either of the hemicelluloses (B_1) and (B_2) of Buston and Chambers, but the most striking difference is the high proportion of *d*-glucose (89%) in the mixture of sugars in the hydrolysis products of the polysaccharide, galactose amounting to but 7·6% and mannose 3%. Furthermore the uronic acid appeared to be not *d*-galacturonic acid but *d*-glucuronic acid. Such large differences in properties can be explained in a variety of ways : (*a*) unsatisfactory fractionation, (*b*) hemicelluloses present derived from the fungus as well as from the algal cell walls, (*c*) variation due to the age of the lichens investigated, which may be accentuated by the extremely slow growth period and variations in geographical or climatic conditions.

It may also be recalled that Ulander and Tollens (*Ber.*, **1906**, **39**, 401) obtained glucose in quantity by the hydrolysis of *Cetraria islandica* after the removal of lichenin, and but little mannose and galactose, but showed that the hydrolysis of " Reindeer " mosses gave chiefly galactose and mannose.

The methylated hemicellulose (I) was divided arbitrarily by fractional precipitation from chloroform solution by light petroleum into four fractions, the properties of which (after remethylation in some cases) are recorded in Table I together with those of methylated lichenin.

TABLE I.

	OMe, %.	$[\alpha]_D^{13°}$ in $CHCl_3$.	$\eta_{sp.}^{25°}$.	*c*.	Apparent mol. wt., $K_m = 1 \times 10^{-3}$.
A	40·5	—	0·428	0·3115	28,000
B	43	+11°	0·771	0·3065	51,000
C	43	+ 2·5	0·767	0·3635	42,000
D	41	− 2	0·209	0·3440	12,000
Methylated lichenin	43	−12	0·479	0·3045	32,000

It is not claimed that the apparent molecular weights are absolute values, but they are tabulated in this form for ease of comparison (cf. Haworth, Heath, and Peat, J., 1942, 57).

The composition of the substance (I) is clearly not uniform and it is highly probable that the individual fractions must also represent mixtures; fraction (B) and (C) appear to be of higher and (D) of lower molecular

weight than methylated lichenin. In order to attempt to gain some idea of the basic composition of the hemicelluloses each fraction was subjected to methanolysis and the products were studied. The bulk of the methylated methylglycosides in every case were to be found in a middle fraction (80—90% of the total distillate), which on complete methylation and hydrolysis yielded tetramethyl glucopyranose, thus confirming the view that glucose was the predominant building unit in these hemicelluloses. The corresponding trimethyl glucose prepared by hydrolysis of this middle fraction in each case yielded crystalline 2 : 3 : 6-trimethyl glucose. Each fraction also yielded a crystalline anilide (8—18%), m. p. 162—166°, which proved to be 2 : 4 : 6-*trimethyl glucose anilide*, since it readily gave a crystalline trimethyl glucose, m. p. 124—126°, which gave tetramethyl glucopyranose on methylation and hydrolysis, a trimethyl β-methylglucoside, m. p. 71° (cf. Oldham, *J. Amer. Chem. Soc.*, **1934**, **56**, 1360), and a crystalline amide, m. p. 99°, which gave a negative Weerman reaction (cf. Barker, Hirst, and Jones, J., **1938**, 1696). The other possibilities it was necessary to envisage were 2 : 3 : 4- and 3 : 4 : 6-trimethyl glucoses and the method of Barker, Hirst, and Jones (*loc. cit.*) was used to estimate these. The proportion of 2 : 3 : 4-trimethyl glucose was estimated by the method of Oldham and Rutherford (*J. Amer. Chem. Soc.*, **1932**, **54**, 366) and the Weerman reaction was employed to determine the amount of trimethyl glucose with a free hydroxyl group on C_2. The proportion of 2 : 3 : 6-trimethyl glucose was estimated from the magnitude of the change in rotation of the mixture in 2% methyl-alcoholic hydrogen chloride, and the proportion of 2 : 4 : 6-trimethyl glucose by difference. Great precision is not claimed for these figures, especially the latter, but they are probably correct to 5% (Table II).

TABLE II.

Trimethyl glucoses, %, in main fractions of hydrolysed methylated hemicellulose I.

	2 : 3 : 4-.	2 : 3 : 6-.	2 : 4 : 6-.	3 : 4 : 6-.
A	31	30	25 (13)	14
B	13	29	8 (6)	50
C	9	47	5 (7)	39
D	6	50	10 (13)	34

Figures in parentheses denote yields calculated from the yield of anilide.

From (A) a small quantity of tetramethyl *d*-galactopyranose anilide was isolated (3·5% as the methyl-glycoside), showing that a non-reducing terminal group of *d*-galactopyranose was present in this fraction.

From (B) a small quantity (2·5%) of a fully methylated methylglycoside was isolated. This proved to be a mixture of 2 : 3 : 4 : 6-tetramethyl *d*-glucose and 2 : 3 : 4 : 6-tetramethyl *d*-galactose as shown by the isolation of the crystalline anilides. This hemicellulose fraction must therefore have a branched-chain structure with at least two branches terminated by *d*-glucopyranose and *d*-galactopyranose units respectively.

The results of this investigation may be interpreted in at least two different ways. First, hemicellulose (I) could be a mixture of at least four polysaccharides differing mainly by reason of the different linkages between the β-*d*-glucose residues (1 : 2-, 1 : 3-, 1 : 4- or 1 : 6-), or secondly that we have a mixture of polysaccharides in each of which a mixture of linkages is present. Hitherto the linkage of glucose units in polysaccharides built up of glucose has been found to be uniform, the 1 : 4-type in cellulose, starch, glycogen and lichenin, 1 : 3 in laminarin (Barry, *Sci. Proc. Roy. Dublin Soc.*, **1939**, **22**, 66), and the 1 : 6-type in the dextran produced from sucrose by *Leuconostoc Dextranicum* (Peat *et al.*, J., **1939**, 581). On the other hand a mannan from yeast has been shown to be made up of one type of unit, *viz.*, mannose, linked in three different ways, 1 : 2-, 1 : 3-, and 1 : 6- (Haworth, Heath, and Peat, J., **1941**, 833), and there is no valid reason to doubt the possibility that such mixed linkages could be present in the polysaccharides discussed here. The presence of glucopyranose units linked through C_1 and C_2 has not been previously reported, but the above results show that almost as many are linked in this way as through C_1 and C_4.

EXPERIMENTAL.

Isolation and Purification of the Hemicelluloses.—Iceland moss (1 kg., dry weight) containing 15% of moisture was twice extracted with 1·5% sodium carbonate solution (10 l.) and twenty times with boiling water for 4 hours (15 l. each time) until the extracts on evaporation and hydrolysis were non-reducing to Fehling's solution. The residue (366 g.), dried at 70°/12 mm., was twice extracted at room temperature with 4% sodium hydroxide solution (16·1 l.), and as much as possible of the liquor separated by filtration through muslin. To a solution thus obtained (8·3 l.), after acidification with acetic acid, alcohol (9·2 l.) was added, and the brown jelly separated in a centrifuge. The material was then dissolved in 4% sodium hydroxide solution (5·14 l.) and centrifuged; Fehling's solution (1·28 l.), followed by alcohol (5 l.), was added, and the precipitated copper complex collected on muslin. This was then treated with 2N-hydrochloric acid (1 l.), and the hemicelluloses again precipitated with alcohol (2·5 l.). The product was dissolved in hot dilute sodium hydroxide solution (4·8 l.) and acidified with acetic acid. By the addition of alcohol (3440 c.c.) the bulk (89%) of the hemicelluloses (I) was precipitated and removed in a centrifuge. The addition of more alcohol (2·5 l.) precipitated the remainder (II). The bulk of the material was washed twice and kept moist, with alcohol; a portion for direct investigation was washed with alcohol and ether and dried over phosphoric oxide in a vacuum.

Hemicellulose (I) (Found: ash, 0·6%; uronic acid, 4·95%; pentose, nil). (II) (Found: uronic acid, 8·5%; pentose, nil).

Hydrolysis of (I).—(I) (4·00 g.) was heated with 3·7% sulphuric acid (100 c.c.) for 3·5 hours. Insoluble matter (0·663 g.) was removed, and the filtrate neutralised with barium carbonate, heated, and evaporated to dryness at 45°/12 mm. The resulting viscous syrup in water (8 c.c.) was poured into alcohol (2·2 l.), and the resulting flocculum collected on a Gooch filter (0·3281 g.). The alcoholic filtrate gave a glass (2·72 g.) on evaporation.

The Estimation of Artificial Mixtures of Mannose, Glucose, and Galactose.—Mannose (0·052 g.) and glucose (0·376 g.)

in water (15 c.c.) and alcohol (15 c.c.) were treated with phenylmethylhydrazine (0·75 g.) and acetic acid (1·5 c.c.). No precipitate resulted.

Galactose (0·038 g.), mannose (0·048 g.) and glucose (0·632 g.) in water (22 c.c.) and alcohol (22 c.c.) were treated with phenylmethylhydrazine (1·1 c.c.) and acetic acid (2·2 c.c.). After 48 hours at 10° the precipitate was washed with alcohol (3 c.c.) and dried at 105°. The yield of galactosephenylmethylhydrazone corresponded to 3% of galactose instead of 5·2%.

Mannose (0·400 g.) and galactose (0·712 g.) in water (11 c.c.) were treated with phenylhydrazine (0·8 c.c.), acetic acid (0·8 c.c.) and water (2 c.c.). After 48 hours at 0° the precipitate was washed with ice-water (200 c.c.), alcohol (10 c.c.) and ether (10 c.c.) and dried at 105°. The yield of mannosephenylhydrazone corresponded to 34·5% of mannose instead of 35·6%.

Mannose (0·035 g.), galactose (0·028 g.) and glucose (0·49 g.) in water (60 c.c.) were treated with phenylhydrazine (1·25 c.c.), acetic acid (1·25 c.c.) with sodium acetate (1 g.) and sodium bisulphite (0·05 g.) for 1 hour at 160°. After 24 hours the precipitate was collected and washed with dilute acetic acid and water. The yield of osazone corresponded to 55% of the weight of glucose present.

The Estimation of the Hexoses in the Hydrolysis Products of (I).—This was carried out according to the above methods, the appropriate factors being applied [Found: Galactose, 7·6; mannose, 3·0; glucose 96% (mean of two determinations)].

Hydrolysis of (I) *with* 15% *Sulphuric Acid.*—(I) (7·3 g.) was treated at 100° for 24 hours with sulphuric acid (125 c.c., 15%). The insoluble residue (0·43 g.) was removed, and the solution neutralised with the calculated quantity of barium hydroxide solution in the presence of charcoal. After evaporation to 5 c.c., and precipitation in alcohol (2·5 l.), a white flocculent precipitate (0·95 g.) was separated in a centrifuge, and was washed with alcohol and ether and dried in a vacuum over phosphoric oxide; $[\alpha]_D^{18°}$ +13° in water (*c*, 1·1). Oxidation with 6N-nitric acid at 60° gave no mucic acid. Treatment with *p*-bromophenylhydrazine gave a yellow precipitate characteristic of *d*-glucuronic acid (cf. Hirst and Jones, J., 1938, 1179, who record $[\alpha]_D^{18°}$ +15° for the barium *d*-glucuronate).

Acetylation of (I).—(I) (10 g.) which had been kept in alcohol was suspended in pyridine (150 c.c.); acetic anhydride (100 c.c.) was added in five batches at 10-minute intervals with mechanical stirring, and the mixture maintained for 3 hours at 100°. The solution was set aside for 48 hours and filtered through glass wool; the precipitate produced by addition of a large volume of water was washed in running water for 24 hours (yield 14 g.). The product had $[\alpha]_D^{18°}$ *ca.* −10° in chloroform [Found: $CH_3{\cdot}CO$, 43·5%; $\eta_{sp.}^{25°}$ 0·436 (*c*, 0·3000); M_v = 36,400, K_m being taken as 9×10^{-4}]. For lichenin acetate $\eta_{sp.}^{25°}$ 0·514 (*c*, 0·3525), M_v = 36,400. M_v represents apparent molecular weight only. The acetate was non-homogeneous and was fractionated after methylation.

Deacetylation and Methylation.—Hemicellulose (I) acetate containing moisture (70%) (dry weight 30 g.), dissolved in boiling acetone (1·2 l.), was treated with methyl sulphate (600 c.c.) and sodium hydroxide solution (1500 c.c., 30%) with vigorous stirring in the usual way at 40—45°. The temperature was then raised slowly to remove acetone and the solution was finally heated at 75—80° for 1 hour. The brown solid admixed with sodium sulphate was collected hot and washed with boiling water. All the available acetate (110 g.) was thus twice methylated; two batches were then united and again subjected to two methylations. Yield, 64 g.

Fractionation of Methylated Hemicellulose (I).—The above product was dissolved in chloroform (1500 c.c.), dried with anhydrous sodium sulphate, and filtered. Light petroleum (8·8 l.) (b. p. 60—80°) was added with vigorous stirring to yield (A) (14·06 g.), which was separated in a centrifuge. Light petroleum (1·5 l.) precipitated (B) (15·76 g.), and a further 2·3 l. (C) (15·46 g.). The solution on evaporation yielded (E) (18·72 g.). (A), (C) and (E) were remethylated. The properties are recorded in Table I.

Hydrolysis of (A) *and Fractionation.*—(A) (8·4 g.) was heated for two 15-hour periods at 70° with methyl-alcoholic hydrogen chloride (170 c.c., 5%). Neutralisation with silver carbonate and removal of solvent yielded a syrup (7 g.), which was separated into two fractions by distillation at 0·05 mm.; these were redistilled from a flask fitted with a vacuum-jacketed column [except for fractions (IV) and (V)]. In this way five fractions were obtained as follows (all the b. p.'s in this and subsequent distillations refer to bath temperatures): (A1) 0·74 g., b. p. 135°/0·04 mm., $n_D^{20°}$ 1·4526, OMe 53·5%; (A2) 1·26 g., b. p. 145—160°/0·04 mm., $n_D^{20°}$ 1·4593; (A3) 0·58 g., b. p. 168—180°/0·02 mm., $n_D^{20°}$ 1·4585; (A4) 2·16 g., b. p. 160—165°/0·02 mm., $n_D^{20°}$ 1·4591, OMe 51·2%; (A5) 0·8 g., b. p. 165—175°/0·02 mm., $n_D^{20°}$ 1·4632, OMe 47·8%.

(A1) was slowy refractionated, yielding 0·2 g., $n_D^{20°}$ 1·4511. This on hydrolysis with N-sulphuric acid at 100° for 10 hours yielded a sugar (0·165 g.), which was treated with aniline (0·08 c.c.) in alcohol (0·8 c.c.) at 80° for 2 hours. The crystals obtained were recrystallised from ether–light petroleum yield (0·024 g.); m. p. 196°, unchanged by tetramethyl *d*-galactopyranose anilide, $[\alpha]_D^{20°}$ −80° in acetone (*c*, 0·4).

Investigation of the Trimethyl Methylglycosides.—(A4) was methylated several times with methyl iodide and silver oxide. The product on hydrolysis with N-sulphuric acid and anilide formation yielded tetramethyl glucopyranose anilide in good yield, m. p. 138°, not depressed by an authentic specimen.

Fractions (A3) and (A4) (combined) were hydrolysed with N-sulphuric acid for 9 hours at 95—100°, and the sugars isolated in the usual way.

Isolation of 2 : 4 : 6-*Trimethyl Glucose.*—(A3) and (A4) (combined) were hydrolysed to give a reducing syrup (1·4 g.), which on heating with aniline (2 c.c.) and alcohol (5 c.c.) at 95° for 3 hours gave a crystalline *anilide* after several days, two crops of which (0·24 g.) were removed. The anilide after recrystallisation from alcohol had m. p. 162—166°, $[\alpha]_D^{15°}$ −113° in methyl alcohol (*c*, 1·0), constant, 24 hours. (Found: C, 60·1; H, 7·8; OMe, 30·1; N, 5·2. $C_{15}H_{23}O_5N$ requires C, 60·6; H, 7·8; OMe, 31·3; N, 4·7%).

Repeated attempts to prepare crystalline anilides from 2 : 3 : 6- and 3 : 4 : 6-trimethyl glucose were unsuccessful.

Hydrolysis for 2 hours with sulphuric acid (3%) at 95°, followed by neutralisation with barium carbonate, extraction with ether, and removal of water at 40°/15 mm., gave a sugar (60%) which crystallised spontaneously; recrystallisation from dry ether gave 2 : 4 : 6-trimethyl α-*d*-glucose, m. p. 124—126°, $[\alpha]_D^{15°}$ +109° (initial), +74° (8 hours, constant) in water (*c*, 1·0); $[\alpha]_D^{15°}$ +107° (initial), +70° (24 hours, constant) in 2% methyl-alcoholic hydrogen chloride (*c*, 1·01) (Found: C, 48·5; H, 8·1; OMe, 41·2. Calc. for $C_9H_{18}O_6$: C, 48·7; H, 8·1; OMe, 41·9%).

Three methylations with methyl iodide and silver oxide and hydrolysis gave quantitatively tetramethyl glucopyranose, m. p. 88° alone or mixed with an authentic specimen.

A small quantity of the sugar was oxidised with bromine, and the acid esterified with diazomethane; the amide obtained on treatment with ammonia had m. p. 99°, $[\alpha]_D^{15°}$ +47° in water (*c*, 0·5), and gave a negative Weerman reaction.

The sugar (0·1 g.) was acetylated with pyridine and acetic anhydride, the acetate treated with hydrogen bromide–acetic acid, and the product shaken in methanol with silver carbonate. Deacetylation gave a crystalline glucoside (0·1 g.), which after recrystallisation from light petroleum had m. p. 71°, $[\alpha]_D^{15°}$ −26° in water (*c*, 1·0) (Found: C, 50·4; H, 8·5; OMe, 51·8. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5; OMe, 52·5%).

Investigation of Position C_6.—(A4) (0·8 g.) in pyridine (1 c.c.) was treated with *p*-toluenesulphonyl chloride (1 g.) and kept at room temperature for 48 hours. Water was then added, the solution extracted with benzene, and the extract washed with dilute hydrochloric acid, aqueous sodium bicarbonate and water and dried over anhydrous sodium sulphate.

Removal of solvent gave a syrup (1·135 g.), which was heated with anhydrous sodium iodide (1·2 g.) in acetone (11 c.c.) at 100° for 2 hours in a sealed tube. The precipitated sodium *p*-toluenesulphonate (0·1752 g.) was washed with dry acetone. This indicated that 31% of the starting material was unsubstituted on C_6 (Calc. from 1·135 g. of 6-tosyl-2 : 3 : 4-trimethyl methylglucoside : 0·5647 g. of sodium *p*-toluenesulphonate). With later fractions the iodo-compound was decomposed with silver nitrate in methyl cyanide, and the silver iodide weighed.

When 3-tosyl 2 : 4 : 6-trimethyl methylgalactoside (0·1270 g.) was treated as described above, no sodium *p*-toluenesulphonate or silver iodide was obtained.

Investigation of Position C_2.—A portion of the hydrolysed fractions (A3) and (A4) (combined) was oxidised with bromine at room temperature until it was non-reducing. The solution was then repeatedly extracted with chloroform after removal of bromine, and after drying over sodium sulphate and removal of solvent lactone formation was completed at 100°/15 mm. This was followed by distillation at 125—150°/0·06 mm. to yield a lactone (0·25 g.), $n_D^{19°}$ 1·4655. Immediately after distillation the lactone was treated with methyl-alcoholic ammonia and kept at 0° for 2 days; removal of solvent gave an amide, $[\alpha]_D^{19°}$ +50·5° in methyl alcohol (*c*, 3·8). The amide (0·2715 g.) was dissolved in water (7 c.c.), standard sodium hypochlorite (4·7 c.c.) (Weerman, *Rec. Trav. chim.*, 1917, **36**, 16) added, and the mixture kept at 0° for 3 hours. Excess of hypochlorite was destroyed by sodium thiosulphate, anhydrous sodium acetate (2·7 g.) added, and then semicarbazide hydrochloride (0·54 g.) was added to the filtered solution. After 12 hours the precipitated hydrazodicarbonamide was collected, washed with water (2 c.c.), and dried over phosphoric oxide. Yield, 0·0144 g. of hydrazodicarbonamide, m. p. 256°, *i.e.*, 14% of the practical yield [75% of the theoretical yield (see below)], so 14% of (A3) and (A4) is unsubstituted on C_2.

A control experiment with *d*-gluconamide (0·2072 g.) carried out under identical conditions gave hydrazodicarbonamide, m. p. 256° (0·0958 g.), *i.e.*, 76·4% of the theoretical. This was twice repeated. 3 : 4 : 6-Trimethylgluconamide (0·1976 g.) gave hydrazodicarbonamide (0·0736 g.), *i.e.*, 75% of the theoretical.

Proportion of 2 : 3 : 6-*Trimethyl Methylglucosides in* (A).—Hydrolysed (A3) and (A4) (combined) showed $[\alpha]_D^{20°}$ +70° (initial), +39·7° (constant value after 24 hours) in 2% methyl-alcoholic hydrogen chloride (*c*, 0·4).

Authentic 2 : 3 : 6-trimethyl glucose showed $[\alpha]_D^{18°}$ +70° (initial), −32° (constant value after 24 hours) (*c*, 0·4).

3 : 4 : 6-Trimethyl glucose prepared according to Reynolds (J., 1933, 225) and Haworth, Hirst, and Panizzon (J., 1934, 154) showed $[\alpha]_D^{20°}$ +69° (initial, constant) in 2% methyl-alcoholic hydrogen chloride (*c*, 0·63).

The equilibrium rotation of 2 : 4 : 6-trimethyl glucose in the same solvent was found to be $[\alpha]_D^{15°}$ +70°, and the rotation of 2 : 3 : 4-trimethyl glucose in methanol is given as +69° (Irvine and Oldham, J., 1921, **119**, 1744). It being assumed that the presence of the other methylated glucoses does not affect the final equilibrium of 2 : 3 : 6-trimethyl glucose in methyl-alcoholic hydrogen chloride to any great extent, since the equilibrium rotations of the other three possibilities are *ca.* +70°, the proportion of 2 : 3 : 6-trimethyl glucose in the mixture concerned is 30%.

It is concluded, therefore, that about 85% of the methylglycosides obtained by the hydrolysis of (A) are trimethyl methylglucosides made up of the following trimethyl glucoses : 2 : 3 : 4- (31%), 3 : 4 : 6- (14%), 2 : 3 : 6- (30%), and 2 : 4 : 6- (by difference, 25%). The isolation of tetramethyl galactopyranose anilide shows that *d*-galactose end groups were present to the extent of about 3·5%.

Hydrolysis and Fractionation of (B).—The methylated compound (15·31 g.) was hydrolysed as described for (A) to give a mixture of glycosides (16·54 g.), $[\alpha]_D^{18°}$ +48·8° in methanol (*c*, 0·95). Distillation from an ordinary flask gave 15·52 g. of distillate, which was divided into three fractions, b. p. 93—110°/0·01 mm., 110—127°/0·01 mm., and 127—150°/0·01 mm. These were redistilled through a vacuum-jacketed column to give the following : (B1), 0·36 g., b. p. 126—141°/0·005 mm., $n_D^{12°}$ 1·4492, OMe 57·3%; (B2) 1·68 g., b. p. 141—153°/0·005 mm., $n_D^{12°}$ 1·4560; (B3), 3·24 g., b. p. 153—160°/0·005 mm., $n_D^{12°}$ 1·4622, OMe 50·4%; (B4) 7·18 g., b. p. 150—155°/0·01 mm., $n_D^{12°}$ 1·4615; (B5) 1·14 g., b. p. 158—173°/0·01 mm., $n_D^{12°}$ 1·4610; (B6) 0·90 g., b. p. 165—175°/0·01 mm., $n_D^{12°}$ 1·4654; (B7) 0·10 g., b. p. 175—195°/0·01 mm., $n_D^{12°}$ 1·4701, OMe 45·6%; (B8) 1·00 g., residue, $n_D^{12°}$ 1·4838.

Isolation of Tetramethyl Galactopyranose Anilide and Tetramethyl Glucopyranose Anilide from (B1).—On distillation (B1) gave [B1(*a*)] 0·11 g., b. p. 85—88°/0·04 mm., $n_D^{16°}$ 1·4470, $[\alpha]_D^{12°}$ +63° in water (*c*, 0·3); [B1(*b*)] 0·15 g., b. p. 95—100°/0·04 mm., $n_D^{16°}$ 1·4481, OMe 59·2%.

[B1(*a*)] was hydrolysed to give a syrup (0·07 g.), which yielded tetramethyl *d*-galactopyranose anilide on suitable treatment, m. p. 198°, not depressed by an authentic specimen.

[B1(*b*)] on treatment in a similar way gave an anilide (0·03 g.), m. p. 196°, identical with tetramethyl *d*-galactopyranose anilide (Found : C, 61·5; H, 7·9. Calc. for $C_{16}H_{25}O_5N$: C, 61·7; H, 8·1%).

On standing for some time more crystals were deposited which on recrystallisation had m. p. 136°, unchanged on admixture with tetramethyl glucopyranose anilide.

Investigation of the Trimethyl Methylglycosides.—(B3) (0·61 g.) was twice methylated with methyl iodide and silver oxide, and the product distilled to give a mobile oil (0·5 g.), b. p. 85—90°/0·01 mm., $n_D^{16°}$ 1·4472 (Found : OMe, 61·0. Calc. for $C_{11}H_{22}O_6$: OMe, 62%).

The oil was hydrolysed for 7 hours with N-sulphuric acid (15 c.c.); the sugar, $[\alpha]_D^{12°}$ +85° in water (*c*, 0·4), isolated in the usual way, crystallised on nucleation with tetramethyl glucopyranose. Anilide formation yielded an anilide, m. p. 136—138°, not depressed on admixture with tetramethyl glucopyranose anilide (Found : C, 61·7; H, 8·2; OMe, 39·6; N, 4·4. Calc. for $C_{16}H_{25}O_5N$: C, 61·7; H, 8·1; OMe, 39·9; N, 4·5%).

Hydrolysis and Fractionation of (C).—Methylated (C) (17·09 g.) was hydrolysed with methyl-alcoholic hydrogen chloride (4%) for 30 hours and with methyl-alcoholic hydrogen chloride (5%) for 45 hours to yield a syrup (15·49 g.), $[\alpha]_D^{11°}$ +96·5° in methanol (*c*, 0·58). Distillation yielded 13·7 g. of glycosides, which were separated into three fractions, b. p. 115—130°/0·03 mm., b. p. 130—145°/0·01 mm., and b. p. 145—180°/0·01 mm., each of which was distilled from a flask through a vacuum-jacketed column as before to yield the following fractions : (C1) 1·20 g., b. p. 132—145°/0·01 mm., $n_D^{17°}$ 1·4538; (C2) 1·79 g., b. p. 145—155°/0·01 mm., $n^{17°}$ 1·4580, OMe 51·7%; (C3) 3·64 g., b. p. 155—165°/0·01 mm., $n_D^{17°}$ 1·4598; (C4) 3·93 g., b. p. 145—175°/0·01 mm., $n_D^{17°}$ 1·4600; (C5), 1·28 g., b. p. 160—170°/0·03 mm., $n_D^{18°}$ 1·4621; (C6) 0·37 g., b. p. 170—195°/0·03 mm., $n_D^{18°}$ 1·4621, OMe 14·78%; (C7) 1·03 g., residue, $n_D^{16°}$ 1·4729.

Fraction (C1). Fraction (C1) was redistilled through the fractionating column and gave [C1(*a*)] 0·44 g., b. p. 142—146°/0·02 mm., $n_D^{18°}$ 1·4558, OMe 51·0%, and [C1(*b*)] 0·76 g., residue.

[C1(*a*)] was redistilled from a small flask, the first two drops having b. p. 92°/0·02 mm., $n_D^{14°}$ 1·4577, OMe 49·5%, indicating the absence of a fully methylated end group. [C1(*a*)] was also heated with 0·1N-potassium hydroxide at 100° for 2·5 hours, but no alkali was used up, showing the absence of an ester group.

[C1(*a*)] was then methylated three times with Purdie's reagents; the product, hydrolysed, and subjected to anilide formation, gave tetramethyl glucopyranose anilide, m. p. and mixed m. p. 136°, in good yield.

Investigation of the Trimethyl Methylglucosides. Fraction (C4).—(C4) was fully methylated by Purdie's method and distillation gave an oil, b. p. 100°/0·03 mm., $n_D^{16°}$ 1·4466, OMe 61·0%, which on hydrolysis and treatment with aniline gave tetramethyl glucopyranose anilide in good yield, m. p. 138°, not depressed by an authentic specimen.

Hydrolysis and Fractionation of (D).—Methylated (D) (17·14 g.) was treated thrice with boiling methyl-alcoholic hydrogen chloride for 45 hours, and the product worked up as before to yield a mixture of glycosides (18·47 g.), $[\alpha]_D^{12°}$

+94° in methanol (*c*, 0·4). Distillation yielded 16·66 g., which were redistilled to give three fractions, b. p. 118—130°/0·03 mm., 132—142°/0·02 mm., 140—150°/0·01 mm. Redistillation as previously described gave 7 fractions: (D1) 0·28 g., b. p. 130—155°/0·03 mm., $n_D^{14°}$ 1·4560, OMe 51·6%; (D2) 3·10 g., b. p. 150—160°/0·03 mm., $n_D^{14°}$ 1·4601; (D3) 6·68 g., b. p. 159—167°/0·03 mm., $n_D^{14°}$ 1·4609; OMe 49·0%; (D4) 3·64 g., b. p. 159—167°/0·03 mm., $n_D^{15°}$ 1·4618; (D5) 1·75 g., b. p. 167—175°/0·03 mm., $n_D^{15°}$ 1·4639; (D6) 0·20 g., b. p. 175—195°/0·03 mm., $n_D^{15°}$ 1·4680, OMe 48·3%; (D7) 0·76 g., residue, $n_D^{14°}$ 1·4828.

Investigation of the Trimethyl Methylglucosides.—A portion (0·25 g.) of (D2) was completely methylated with methyl iodide and silver oxide and on distillation gave an oil, $n_D^{16°}$ 1·4466, OMe 61·0%, which gave tetramethyl glucopyranose anilide in good yield on hydrolysis and suitable treatment, m. p. 138°, not depressed by an authentic specimen.

The hydrolysis and examination of fractions of trimethyl methylglucosides from (B), (C), and (D) were carried out as for (A); the results are in Tables III, IV, V, and VI.

TABLE III.

Investigation of Position C_2.

(1).	(2).	(3).	(4).	(5).
A3 + A4	+50·5°	0·2715	0·0144	14
B3	+54	0·1276	0·0252	52
		0·2082	0·0373	48
C3 + C4	+44	0·1750	0·0259	39
D3 + D4	+45	0·2349	0·0298	34
D3 + D4	—	0·2314	0·0305	35

(1) Fraction number.
(2) $[\alpha]_D^{19°}$ of amide in methanol.
(3) Weight of amide, g.
(4) Yield, g., of hydrazodicarbonamide from (3).
(5) % with unsubstituted OH on C_2.

TABLE IV.

Investigation of Position C_6.

(1).	(2).	(3).	(4).	(5).	(6).
A4	1·135	0·1752	—	—	31
B4	0·980	0·064	—	—	13
B4	—	—	0·6071	0·0514	12
C4	—	—	1·203	0·0718	8·8
D4	—	—	1·03	0·0391	5·6

(1) Fraction number.
(2) Wt. of tosyl derivative, g.
(3) Yield, g., of sodium *p*-toluenesulphonate from (2).
(4) Weight of *p*-toluenesulphonate after treatment with sodium iodide, g.
(5) Yield of silver iodide from (4), g.
(6) % with unsubstituted OH on C_6.

TABLE V.

Investigation of Position C_4.

(1).	(2).	(3).	(4).	(5).	(6).
A3 + A4	—	—	—	+39·7°	30
B3	54	+37·5°	+46·2°	—	29
B4	—	—	—	+40	30
C3	66	+11·5	+33·3	—	50
C4 + C5	—	—	—	+22·5	46·5
D3	95	−24	—	—	—
D3 + D4	—	—	—	+18·7	50

(1) Fraction number.
(2) Crystalline trimethyl glucose, %.
(3) Equilibrium $[\alpha]_D^{18°}$ in methanol–HCl (2%) of crystals.
(4) Equilibrium $[\alpha]_D^{15°}$ in methanol–HCl of residual syrup after removal of crystals.
(5) Equilibrium $[\alpha]_D^{18°}$ of hydrolysed fraction in same solvent.
(6) 2 : 3 : 6-Trimethyl glucose, %.

TABLE VI.

Yields of 2 : 4 : 6-Trimethyl Glucose Anilide.

(1).	(2).	(3).	(4).
A3 + A4	1·4	0·24	17
B4 + B5	1·0	0·09	9
C4 + C5	1·64	0·146	9
D3 + D4	1·44	0·256	18

(1) Fraction number.
(2) Weight of hydrolysed fraction, g.
(3) Yield of anilide, g.
(4) % Yield of anilide.

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KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, October 22nd,* 1942.]

21. *The Mechanism of Indole Formation from Phenacylarylamines. Part I.*

By ALBERT F. CROWTHER, FREDERICK G. MANN, and (in part) DONALD PURDIE.

The conversion of the phenacyl derivatives of primary arylamines into the corresponding 2-arylindoles is dependent on the presence of catalytic impurities (*e.g.*, amine hydrobromides and hydriodides); non-recognition of this factor has invalidated much previous work, and earlier theories of the mechanism of this conversion based on such work are now shown to be incorrect. The behaviour of such phenacyl derivatives when heated alone and in the presence of possible catalysts, and also when heated with primary and secondary arylamines, has been investigated in detail, and an ionic mechanism for the above conversion is suggested.

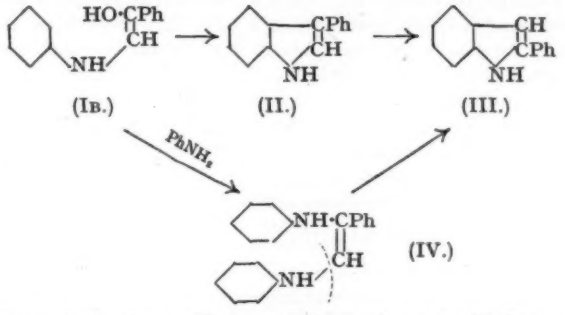
The phenacyl derivatives of secondary arylalkylamines behave entirely differently, giving 3-aryl-1-alkylindoles, which (with one exception) could not be isomerised to 2-aryl-1-alkylindoles. The reaction of these phenacyl derivatives with primary and secondary amines has also been investigated, and these reactions correlated with those of the phenacyl primary amines.

THE mechanism whereby the phenacyl derivatives of aromatic amines undergo cyclisation to give 2-arylindoles has, in spite of much investigation and controversy,* remained obscure. Möhlau (*Ber.*, 1881, **14**, 173; 1882, **15**, 2480) showed that phenacyl bromide when heated with aniline gave 2-phenylindole, the identity of which

* Further references, in addition to those given, are: Wolff, *Ber.*, 1888, **21**, 124; 1889, **22**, 428; Möhlau, *Ber.*, 1892, **25**, 2485; Lachowicz, *Monatsh.*, 1894, **15**, 402; Collet, *Bull. Soc. chim.*, 1897, **17**, 66; Hell and Cohen, *Ber.*, 1904, **37**, 866; Strain, *J. Amer. Chem. Soc.*, 1929, **51**, 269.

was confirmed by Fischer and Schmidt (*Ber.*, 1888, **21**, 1071, 1811), who prepared it also by the action of zinc chloride on acetophenonephenylhydrazone. Möhlau (*loc. cit.*; *Ber.*, 1885, **18**, 165) stated that phenacylaniline, $NHPh{\cdot}CH_2{\cdot}COPh$ (I), the initial product in his reaction, gave 2-phenylindole slowly at room temperature when exposed to the air, more rapidly when confined over sulphuric acid, and readily when dry-distilled or heated with either phosphorus pentachloride or aniline : the reaction with aniline was confirmed by Bischler (*Ber.*, 1892, **25**, 2868). Two theories have been advanced to explain this formation of 2-phenylindole.

(A) The enolic form of (I), *i.e.*, (IB), undergoes normal cyclisation to give 3-phenylindole (II), which in the above circumstances isomerises to 2-phenylindole (III). Fischer and Schmidt (*loc. cit.*) pointed out that this explanation was supported by the fact that 3- was isomerised to 2-phenylindole by heating with zinc chloride, but was weakened by the fact that 3-phenylindole was unaffected by boiling with aniline. (B) Bischler (*loc. cit.*)



stated alternatively that (I), again in the enolic form (IB), condensed with free aniline to give the diamine (IV), which underwent cyclisation with loss of the *original* aniline residue to give 2-phenylindole. Bischler showed that, *e.g.*, both phenacylaniline and phenacyl-*o*-toluidine when heated with aniline gave 2-phenylindole, and that both when heated with *o*-toluidine gave 2-phenyl-7-methylindole, the free amine thus always forming the final indole. This theory was put forward when indoles were obtained by interaction of phenacyl bromide and excess of amine : it is extremely unlikely to apply to the conversion of phenacylaniline alone into the indole when no excess of free aniline is present.

These two theories, which may be termed the isomerisation and the diamine theory respectively, will be considered in turn. Our experiments show that neither can be correct. It should be noted that all this early work concerned phenacyl primary amines with the exception of a brief study of phenacyl-*N*-methylaniline (Staedel, *Ber.*, 1888, **21**, 2197; Culmann, *ibid.* p., 2595), discussed below. We find that the cyclisation of phenacyl secondary amines is, with the exception of this methyl derivative, entirely different from that of the corresponding phenacyl primary amines.

(A) *The Isomerisation Theory.*—It is now clear that early work on the cyclisation of phenacylaniline was invalidated by the use of impure material, which contained traces of the hydrobromide of aniline or of phenacylaniline, which we find to be active catalysts in promoting the formation of 2-phenylindole. Similarly, Japp and Murray (J., 1894, **65**, 889) showed that Bischler and Fireman's claim (*Ber.*, 1893, **26**, 1336) that desylanilide reacted with boiling aniline to give 2 : 3-diphenylindole was true only if a trace of aniline hydrochloride was present : the pure compounds did not interact. Campbell and Cooper (J., 1935, 1208) likewise found traces of hydrogen bromide essential for the formation of, *e.g.*, 2-phenyl-7-methylindole. We find that *pure* phenacylaniline, contrary to Möhlau's statement, is remarkably stable and can be exposed to the air at room temperature for 18 months or distilled under reduced pressure without change. Furthermore, when subjected to dry distillation it gives aniline, diphenacyl, $COPh{\cdot}CH_2{\cdot}CH_2{\cdot}COPh$ and 1 : 2 : 5-triphenylpyrrole : both the origin and identity of the pyrrole are clearly indicated by its ready formation when aniline and diphenacyl undergo condensation in boiling acetic acid solution. When, however, phenacylaniline is heated with traces of many amine hydrobromides and hydriodides and quaternary bromides and iodides at 180° for short periods, it undergoes smooth conversion into 2-phenylindole. Similar treatment with amine hydrochlorides and other salts produces a mixture of aniline and diphenacylaniline, $NPh(CH_2{\cdot}COPh)_2$, or leaves the phenacylaniline unchanged, or gives a viscous indeterminate syrup. The compounds thus tested as catalysts are here listed : in all cases the phenacylaniline was mixed with 0·01 g.-mol. of the compound, and was heated at 180°, usually for 6 minutes (p. 63).

(a) *Causing conversion into 2-phenylindole.* I_2; NH_2Ph,HBr; NH_2Ph,HI; p-$C_6H_4Me{\cdot}NH_2,HBr$; p-$C_6H_4Me{\cdot}NHEt,HBr$; $NHPh_2,HBr$; NMe_2Ph,HI; NMe_3PhI; $NHPh{\cdot}CH_2{\cdot}COPh,HBr$; $NHPh{\cdot}CH_2{\cdot}COPh,HI$; pyridine methiodide, quinoline methiodide and ethiodide; quinaldine methiodide and ethiodide; $AsPh_3,MeI$.

(b) *Causing partial conversion into diphenacylaniline.* $(CO_2H)_2$; NH_2Ph,HCl; $2NH_2Ph,(CO_2H)_2$; $2NH_2Ph,H_2SO_4$; p-$C_6H_4Me{\cdot}NH_2,HCl$; pyridine ethiodide.

(c) *Causing no apparent change.* NH_4Br; NH_4I; $NH_2Ph,CCl_3{\cdot}CO_2H$; NMe_4I; $AsPh_4Br$; $AsPh_4I$; benzoyl peroxide.

(d) *Causing decomposition to viscous uncrystallisable syrups.* $NHPh{\cdot}CH_2{\cdot}COPh,HCl$; $NHPh_2,HCl$; $ZnCl_2$; $AlCl_3$.

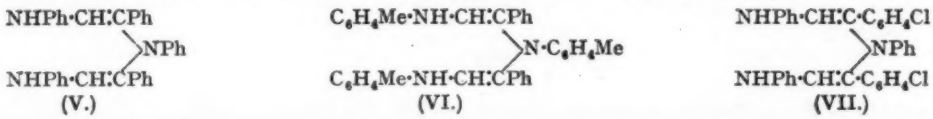
Since 3-phenylindole can be distilled unchanged (b. p. 226°/14 mm.) and is moreover unaffected by heating

with aniline hydrobromide under the above conditions, it clearly cannot be an intermediate in the above formation of 2-phenylindole.

It should be noted that all the compounds in Group (a) give rise under these conditions not only to bromide or iodide ions but also to hydrogen ions. Free iodine will do this by direct iodination of the amine, the amine salts by slight dissociation, the quaternary salts by decomposition (the quinoline and quinaldine salts, in particular, slowly decompose even at room temperature). Pyridine ethiodide in Group (b) and tetramethylammonium iodide and the tetraphenylarsonium salts in Group (c) are, however, very stable and could not give hydrogen ions under these conditions. The lack of catalytic action shown by amine hydrochlorides is, however, in marked contrast to Japp and Murray's results. The negative result with benzoyl peroxide shows that the reaction is not promoted by the "peroxide effect."

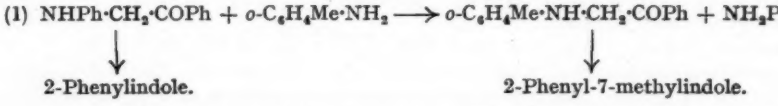
It is noteworthy that pure phenacylaniline when fused with a much greater quantity of zinc chloride (*e.g.*, 10 mols.) at 180° for 15 minutes gave only an amorphous powder from which no crystalline product could be isolated: pure *p*-chlorophenacylaniline gave a similar result. On the other hand, the acetyl derivatives of these two phenacyl compounds were unaffected by this fusion with zinc chloride.

(B) *Bischler's Diamine Theory.*—Bischler (*loc. cit.*) stated that phenacylaniline, when boiled with aniline (9 mols.) for 1 hour, gave 2-phenylindole, but when boiled with *p*-toluidine (10 mols.) gave 2-phenyl-5-methylindole. Many similar results were cited. We find however that pure phenacylaniline reacts with pure aniline to give a triamine, NN-*di*-(β-*phenylamino*-α-*phenylvinyl*)*aniline* (V), and with excess of pure *p*-toluidine to give the homologous *tri*-p-*tolyl* derivative (VI). Phenacylaniline, however, when heated with aniline (2 mols.)



in the presence of aniline hydrobromide (0·01 mol.) gives 2-phenylindole, and when heated with *p*-toluidine (2 mols.) similarly catalysed gives 2-phenyl-5-methylindole. Similarly, phenacylaniline containing aniline hydrobromide (0·01 mol.) reacts with *o*-toluidine (2 mols.) at 180°, giving 2-phenylindole, but with 10 mols. of *o*-toluidine it gives 2-phenyl-7-methylindole. Many similar results are given later (p. 64).

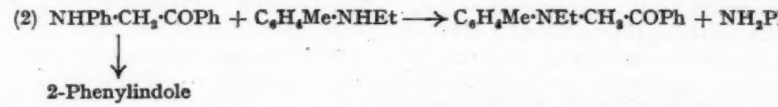
Compounds of the triamine type (V and VI) proved very stable and could not be converted into indoles. There is therefore no evidence for the formation of Bischler's hypothetical diamines from phenacyl primary amines. His results were clearly due to the presence of catalytic impurities. The above results show that a phenacyl primary amine undergoes a slow interchange with a boiling free primary amine (Equation 1), the rate of reaction depending on the active mass and chemical nature of the amine. With pure reagents, the phenacylamine will condense with the free amine present in greatest concentration to give a triamine of type (V) and



(VI). In the presence of catalytic impurities, however, each phenacylamine will tend to cyclise to the corresponding indole. Hence in (1) the presence of a small concentration of *o*-toluidine causes the reaction to go so slowly that the main reaction is direct cyclisation of phenacylaniline to 2-phenylindole: a high concentration of *o*-toluidine increases the rate and thus gives a product which is derived mainly from phenacyl-*o*-toluidine and hence on purification gives 2-phenyl-7-methylindole.

It is now clear why 2-arylindoles can always be prepared by heating phenacyl bromide with an excess of the requisite primary amine, since the phenacyl aryl amine first formed will necessarily be accompanied by equivalent quantities of the amine hydrobromide to catalyse its subsequent conversion into the indole.

The reaction of phenacyl primary amines with secondary amines is also of interest. A mixture of pure phenacylaniline and *N*-ethylaniline (5 mols.) when boiled for 4 hours gave a brown oil from which no crystalline product could be isolated. When, however, a trace of aniline hydrobromide was added to the original mixture, boiling then caused a vigorous evolution of water and the product readily yielded 2-phenylindole. Similarly, a mixture of pure phenacylaniline and *N*-ethyl-*p*-toluidine (2 mols.) with a trace of aniline hydrobromide gave 2-phenylindole and aniline. It is clear, therefore, that in the absence of the aniline hydrobromide, a slow interchange between the phenacylamine and the secondary amine occurred (Equation 2) giving a



complex product containing no indole. In the presence of traces of aniline hydrobromide, however, much of the phenacylaniline underwent direct conversion into 2-phenylindole, the phenacyl-*N*-ethyl-*p*-toluidine being unaffected by this catalyst under these conditions (see p. 61); the yields of 2-phenylindole and of aniline in one experiment with *N*-ethyl-*p*-toluidine were 47% and 27% respectively of those indicated by equation (2).

p-*Chlorophenacylaniline* showed one exceptional property. Collet (*Bull. Soc. chim.*, 1899, **21**, 65) claimed

to have prepared this compound, m. p. 187—188°, by heating *p*-chlorophenacyl chloride with aniline. We find that this interaction, when strictly controlled by brief and very gentle warming, gives the true *p*-chlorophenacylaniline, m. p. 113·5°. More vigorous interaction gives Collet's compound, which is actually an ether formed by loss of water from 2 mols. of the enolic form of the true phenacyl derivative, *i.e.*, it is *di*-(β-*phenylamino*-α-p-*chlorophenylvinyl*) *ether* (VIII) : its structure follows from the fact that it gives a *diacetyl* derivative. This ether (VIII) was unchanged when heated with aniline hydrobromide (0·01 mol.) at 200° for 20 minutes; when fused with zinc chloride at 190—200°, extensive decomposition occurred and no indole could be isolated.

$$\begin{matrix} \mathrm{NHPh{\cdot}CH{:}C{\cdot}C_6H_4Cl} \\ \diagup\!\!\diagdown\mathrm{O} \\ \mathrm{NHPh{\cdot}CH{:}C{\cdot}C_6H_4Cl} \end{matrix}$$
(VIII.)

Before considering possible mechanisms for the above reactions, the behaviour of phenacyl secondary amines when heated similarly with (*a*) possible catalysts, (*b*) primary amines, and (*c*) secondary amines, must be described.

(*a*) Of the many phenacyl secondary amines studied, p-*chlorophenacyl*-N-*ethyl*-p-*toluidine*, $C_6H_4Me{\cdot}NEt{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4Cl$, has been investigated in greatest detail. When exposed to the air at 100° for 7 hours, this gave appreciable quantities of *p*-chlorobenzoic acid; such oxidative fission of the C–C link is apparently inhibited by sodium acetate, since the phenacylamine, mixed with the acetate, remained unchanged at 140—150° after 8 hours. This phenacylamine when boiled with tetralin (b. p. 206°) or with alcoholic zinc chloride (4 mols.), or fused with zinc chloride at 250°, readily gave 3-p-*chlorophenyl*-5-*methyl*-1-*ethylindole*, *i.e.*, simple cyclisation, corresponding in type to the conversion of the enol (IB) into the indole (II), occurred. All attempts—utilising a variety of conditions—to isomerise this 3-*p*-chlorophenylindole, either *in situ* immediately after its formation or after its subsequent isolation, to the corresponding 2-*p*-chlorophenylindole failed (contrast B.P. 496657). Similar results regarding the cyclisation and attempted isomerisation were obtained with several other phenacyl secondary amines. The only exception was phenacyl-*N*-methylaniline, which, when boiled with alcoholic zinc chloride gave 3-phenyl-1-methylindole, but when fused with zinc chloride gave the 2-phenyl isomeride, as Staedel (*loc. cit.*) and Culmann (*loc. cit.*) had claimed. (Staedel's further claim that alcoholic zinc chloride promotes this isomerisation is incorrect.) As would be expected from these results, 3-phenyl-1-methylindole itself, when fused with zinc chloride, was isomerised to the 2-phenyl compound. It is noteworthy, however, that *p*-chlorophenacyl-*N*-methylaniline, when either boiled with alcoholic zinc chloride or fused with anhydrous zinc chloride, gave only 3-p-*chlorophenyl*-1-*methylindole* : the isomerisation of 3-phenyl-1-methylindole is apparently determined, therefore, both by the nature of the 1-alkyl group and by the absence of substituents in the 3-aryl group. We are now investigating this point in greater detail.

It is particularly noteworthy that phenacyl-*N*-ethylaniline was unaffected by heating with *N*-ethylaniline hydrobromide (0·01 mol.) at 180° for 10 minutes, and *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine was unchanged by similar treatment with *N*-ethyl-*p*-toluidine hydrobromide (0·01 mol.) : the marked catalytic action of these salts on phenacyl primary amines is thus completely absent with the corresponding secondary amines.

(*b*) When phenacyl-*N*-ethylaniline was heated with aniline (1·5 mols.) at 150° for 8 hours, free *N*-ethylaniline and the triamine (V) were obtained; similarly, *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine with aniline yielded *p*-chlorophenacylaniline and the triamine (VII), *i.e.*, NN-*di*-(β-*phenylamino*-α-p-*chlorophenylvinyl*)-*aniline*. It follows that here again a double decomposition occurs (Equation 3), and that the phenacyl primary

$$(3)\ \mathrm{NPhEt{\cdot}CH_2{\cdot}COPh + NH_2Ph \longrightarrow NHPh{\cdot}CH_2{\cdot}COPh + NHPhEt}$$
$$\downarrow \mathrm{NH_2Ph}$$
Triamine (V)

amine thus formed condenses with the excess of primary amine as already described (p. 60) to give the corresponding triamine.

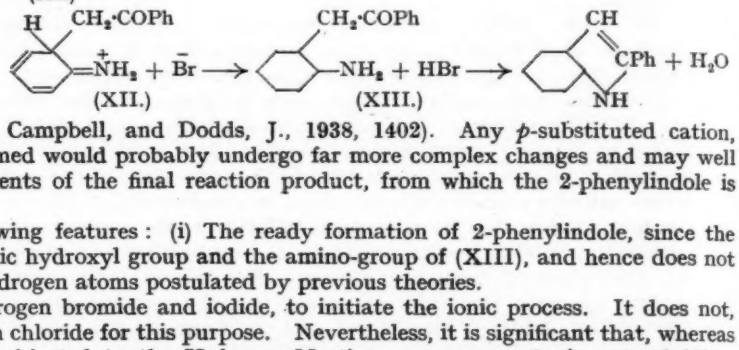
(*c*) To study the interaction of secondary amines with phenacyl secondary amines, mixtures of *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine and free *N*-ethyl-*p*-toluidine have been investigated in greatest detail. This mixture, in equimolecular proportion, when exposed to the air and heated at 100° for 7 hours, gave much *p*-chlorobenzoic acid and 4 : 4′-dichlorobenzil, the fission of the $CH_2{\cdot}CO$ link being thus again evident. When, however, this mixture was heated in a closed vessel at 140—150° for 7 hours, there was formed, in addition to the above products, p-*chloro*-(αβ-*bis*-p-*tolylethylamino*)*vinylbenzene* (IX). This is the only diamine of Bischler's type obtained in this investigation : it was extremely stable, and could not be converted into an indole in spite of many attempts with various reagents. Its formation was completely inhibited by the presence of sodium acetate in the original mixture, only the acid and the diketone being then isolated.

$$\begin{matrix} \mathrm{C_6H_4Me{\cdot}NEt{\cdot}CH{:}C{\cdot}C_6H_4Cl} \\ \mathrm{NEt{\cdot}C_6H_4Me} \end{matrix}$$
(IX.)

In contrast to these results, however, when *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine was boiled with an excess (4 mols.) of *N*-ethylaniline, *N*-*iso*butylaniline, or *N*-ethyl-*p*-toluidine, 3-*p*-chlorophenyl-5-methyl-1-ethylindole was obtained in each case. When *p*-chlorophenacyl-*N*-ethylaniline was similarly treated with each of these three secondary amines, 3-p-*chlorophenyl*-1-*ethylindole* was always formed. It is clear, therefore, that at the higher temperature simple cyclisation of the phenacyl secondary amine to the corresponding 3-arylindole occurs, and is independent of the presence of free secondary amines. This is the main reaction : the formation of the diamine—involving a lower temperature and a smaller proportion of secondary amine—must be regarded as exceptional.

Consideration of the above results strongly suggests that the conversion of phenacyl primary arylamines into 2-arylindoles is closely akin to the Hofmann–Martius rearrangement of alkyl anilines and is governed by an ionic mechanism parallel to that suggested by Hickinbottom (J., 1934, 1700) for the latter rearrangement. As the salts which act as catalysts for the conversion of phenacylaniline into 2-phenylindole [Group (a), p. 59] can all give varying quantities of hydrogen bromide or iodide by dissociation or decomposition (see p. 60), we suggest that the first stage consists in the formation of small quantities of the phenacylanilinium cation (X), which on heating gives aniline and the phenacyl ion (XI). The latter then adds on to the aniline to give the *o*-substituted cation (XII), and probably also simultaneously to give the *p*-substituted isomeride.* The cation (XII) then loses a proton to give phenyl *o*-aminobenzyl ketone (XIII), which in turn cyclises with loss

$$\underset{\text{(X.)}}{\overset{+}{N}H_2Ph\cdot CH_2\cdot COPh} + \bar{B}r \longrightarrow NH_2Ph + \underset{\text{(XI.)}}{\overset{+}{C}H_2\cdot COPh} + \bar{B}r \longrightarrow$$



of water to 2-phenylindole (Womack, Campbell, and Dodds, J., 1938, 1402). Any *p*-substituted cation, isomeric with (XII), which may be formed would probably undergo far more complex changes and may well be responsible for the viscous constituents of the final reaction product, from which the 2-phenylindole is isolated by crystallisation.

This mechanism explains the following features: (i) The ready formation of 2-phenylindole, since the ultimate cyclisation is between the enolic hydroxyl group and the amino-group of (XIII), and hence does not involve the replacement of nuclear *o*-hydrogen atoms postulated by previous theories.

(ii) The necessity for traces of hydrogen bromide and iodide, to initiate the ionic process. It does not, however, explain the failure of hydrogen chloride for this purpose. Nevertheless, it is significant that, whereas *N*-methylaniline hydrobromide when subjected to the Hofmann–Martius rearrangement gives *p*-toluidine, yet the hydriodide gives in addition some *o*-toluidine (Hickinbottom, *loc. cit.*); consequently the migration of the phenacyl ion (XI) may be predominantly *para* in the presence of chlorine ions, but become increasingly *ortho* in the presence of bromine and finally iodine ions. Furthermore, the experimental facts show that most amine hydrochlorides [Group (b), p. 59], like the amine salts of other strong acids, promote also an entirely different reaction, *viz.*, the fission of aniline to form diphenacylaniline.

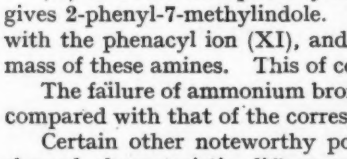
(iii) The fact that acetyl derivatives of phenacyl primary arylamines do not apparently give indoles: clearly these derivatives would not give a cation similar to (X), as the nitrogen atom after acetylation has lost its basic properties. On the other hand, this explanation cannot apply to the similar failure of phenacyl secondary arylalkylamines. It is well known, however, that the Hofmann–Martius rearrangement occurs very much less readily with *NN*-dialkylanilines than with *N*-monoalkylanilines, and in some cases is entirely replaced by other reactions, *e.g.*, dimethylaniline hydrochloride on heating gives methylaniline, and the hydrobromide gives both methylaniline and phenyltrimethylammonium bromide, whilst diethylaniline hydrobromide gives ethylaniline (Hofmann, *Annalen*, 1850, **74**, 137; *Ber.*, 1877, **10**, 600; Staedel, *Ber.*, 1886, **19**, 1947). Hence it is probable that with compounds such as phenacyl-*N*-ethylaniline the Hofmann–Martius rearrangement occurs very slowly (if at all) and that the more rapid cyclisation of the enolic form to give a 3-aryl-1-alkylindole predominates, this reaction being clearly independent of an ionic catalyst.

(iv) The fact that phenacylaniline, heated with excess *o*-toluidine in the presence of aniline hydrobromide, gives 2-phenyl-7-methylindole. There will clearly here be two different primary amines competing for union with the phenacyl ion (XI), and the resulting addition ion (as XII) will depend on the reactivity and active mass of these amines. This of course is merely the ionic interpretation of Equation (1).

The failure of ammonium bromide and iodide to act as catalysts must be attributed to their greater stability compared with that of the corresponding amine salts under the conditions employed.

Certain other noteworthy points have arisen in this investigation. The three types of indole obtained showed characteristic differences with picric acid: the 2-arylindoles gave deep red picrates crystallising readily from benzene; the 2-aryl-1-alkylindoles did not give picrates; the 3-aryl-1-alkylindoles gave deep chocolate-brown (almost black) picrates crystallising well from ethyl alcohol.

p-Chlorophenacyl-*N*-ethyl-*p*-toluidine shows one unique property. The pure pale yellow compound, m. p. 95·5°, is prepared by the interaction of *p*-chlorophenacyl bromide and *N*-ethyl-*p*-toluidine in boiling alcohol in the presence of chalk: when the compound is boiled, however, in alcohol with zinc chloride (1 mol.) it yields a deep yellow *dimer*, m. p. 157·5°. No decisive evidence for the structure of this dimer is at present available. It is possible that the polymerisation has given the dioxan derivative (XIV), and it is significant that Dr. A. Hargreaves and Dr. W. H. Taylor of the Physics Department of the Manchester College of Technology, who have kindly examined the compound crystallographically, find that its molecules do possess the centre of symmetry that the structure (XIV) demands. The existence of a dioxan ring in this compound is not



(XIV.)

* For an example of the migration of a phenacyl group from nitrogen to carbon in a different class of compound, see Thomson and Stevens, J., 1932, 1932.

improbable, as this ring system is known to occur in the " bromodiphenacyls " obtained by the action of sodium ethoxide on phenacyl bromide (Widmann, *Ber.*, 1909, **42**, 3261; *Annalen*, 1913, **400**, 86; Almström, *Ber.*, 1914, **47**, 848).

Campbell and Cooper (*loc. cit.*) and Womack, Campbell, and Dodds (*loc. cit.*) have shown that 2-phenyl-1-methylindole gives a deep green nitroso-compound, which possesses many anomalous properties : they adduce evidence that the nitroso-group is in the 3-position. We find that this is apparently a general reaction for 2-aryl-1-alkyl- and 2-aryl-1 : 5-dialkyl-indoles, and the position of the nitroso-group is thus confirmed. These nitroso-derivatives are of particular value for characterising such indoles, since the latter do not form picrates. We are now investigating the properties of this novel type of nitroso-indole.

In order to prove the identity of some of our 3-aryl-1-alkylindoles, it was necessary to prepare authentic samples of the isomeric 2-aryl analogues by Fischer's hydrazone method. The preparation of the intermediate *as.*-arylalkylhydrazines by reduction of the corresponding nitrosoamines often proved unsatisfactory, and much secondary amine and ammonia were usually formed, particularly with the higher alkyl derivatives. Michaelis (*Ber.*, 1886, **19**, 2448; *Annalen*, 1889, **252**, 266) has, however, shown that phenylhydrazine reacts with sodium to give a derivative $NNaPh{\cdot}NH_2$, which with alkyl halides furnishes the alkyl derivative $NRPh{\cdot}NH_2$ in high yield : the initial reaction with sodium is so violent, however, that the method has been little used. We find that the replacement of sodium by sodamide (Titherley, J., 1897, **71**, 461) in benzene suspension gives a smooth production of the sodium derivative, which without isolation can be treated directly with the alkyl halide. (Substituents in the benzene ring, however, cause very low yields and the method is consequently almost useless with, *e.g.*, *p*-tolylhydrazine.) The *as.*-arylalkylhydrazines thus prepared, when mixed with acetophenone (or other requisite ketone) and then fused with zinc chloride, gave the authentic 2-aryl-1-alkylindoles in good yield.

Experimental.

The names of solvents used for recrystallisation are stated in parentheses after the compounds concerned : when two names are given, as in (acetic acid, alcohol), recrystallisation in each solvent consecutively in this order was performed; when given as in (petrol–benzene), recrystallisation in the mixed solvents was performed.

Phenacyl Primary Amines.—(1) *Preparation.* (For intermediate preparation of phenacyl bromide, *p*-chloroacetophenone, and *p*-chlorophenacyl bromide, see *Organic Syntheses*, 1925, **5**, 19; 1929, **9**, 20; 1939, **19**, 24.) These pure phenacyl derivatives were usually made thus : a solution of phenacyl bromide (100 g.) in alcohol (200 c.c.) was chilled in ice–salt, and the amine (2 mols.) added with vigorous stirring. The bromide, which had crystallised during the initial cooling, rapidly redissolved and was replaced by yellow crystals of the phenacylamine. The mixture was kept cold for 4 hours (occasional stirring) and the phenacylamine then collected, washed with alcohol, mixed with water (1 l.), and vigorously stirred for 3 hours. It was collected, dried, and recrystallised (usually from alcohol).

Phenacylaniline : *hydrobromide*, m. p. 183° (decomp.) (Found : N, 4·9. $C_{14}H_{13}ON,HBr$ requires N, 4·8%); *hydriodide*, m. p. 145° (Found : N, 4·1. $C_{14}H_{13}ON,HI$ requires N, 4·1%); acetyl derivative (alcohol), m. p. 131·5—133° (Found : N, 5·6. Calc. for $C_{16}H_{15}O_2N$: N, 5·5%) (Möhlau, *Ber.*, 1882, **15**, 2470, gives m. p. 126—127°). Phenacyl-2 : 4-dimethylaniline (alcohol), m. p. 96° (Found : C, 80·3; H, 7·4. Calc. for $C_{16}H_{17}ON$: C, 80·3; H, 7·2%) (Kunckell, *Ber.*, 1897, **30**, 575). p-*Chlorophenacylaniline* requires particular care to avoid contamination with the ether (VIII) (p. 65) : aniline (4 g., 2 mols.) was added to a suspension of powdered *p*-chlorophenacyl bromide (5 g., 1 mol.) in alcohol (40 c.c.), and the mixture shaken and warmed very gently until the bromide had dissolved; cooling in ice water for 20 mins. gave yellow needles of the aniline (alcohol), m. p. 113—115°; 2·5 g. (Found : C, 68·4; H, 5·1; N, 5·85; Cl, 14·7; *M*, ebullioscopic in 1·22% acetone solution, 261; in 3·86% solution, 259. $C_{14}H_{12}ONCl$ requires C, 68·4; H, 4·9; N, 5·7; Cl, 14·7%; *M*, 245·6); the filtrate on standing deposited the ether (VIII). The *acetyl* derivative formed colourless crystals (alcohol), m. p. 143° (Found : C, 67·0; H, 5·2; N, 5·2; Cl, 12·8. $C_{16}H_{14}O_2NCl$ requires C, 66·8; H, 4·9; N, 4·9; Cl, 12·4%). p-*Chlorophenacyl*-p-*toluidine* (alcohol), m. p. 148—150° (Found : N, 5·6. $C_{15}H_{14}ONCl$ requires N, 5·4%). p-*Chlorophenacyl*-2 : 4-*dimethylaniline* (alcohol), m. p. 117° (Found : N, 5·4. $C_{16}H_{16}ONCl$ requires N, 5·1%). These phenacylamines varied in colour from pale cream to bright yellow.

(2) *Dry distillation.* (i) Pure phenacylaniline when heated at 12 mm. distilled unchanged, b. p. 208—210°. (ii) When refluxed at 760 mm. for 10 mins. and then distilled at 12 mm., it gave water, aniline (yield, 50% calculated on complete recovery of original aniline), and finally a fraction, b. p. 220—240°/12 mm., which readily solidified. This fraction, crystallised from benzene, gave white crystals, m. p. 127—206°; these were extracted with a small quantity of boiling acetone and the undissolved residue, crystallised from acetic acid, gave 1 : 2 : 5-triphenylpyrrole, m. p. 233—233·5° (Found : C, 89·2; H, 6·5; N, 4·9. Calc. for $C_{22}H_{17}N$: C, 89·4; H, 5·8; N, 4·75%). The acetone mother-liquor was allowed to evaporate, and the final crop gave diphenacyl (acetic acid), m. p. 143—146° (Found : C, 80·7; 6·2. Calc. for $C_{16}H_{14}O_2$: C, 80·7; H, 5·9%). Kapf and Paal (*Ber.*, 1888, **21**, 3056) give m. p.'s 228—229° and 144—145° respectively for these compounds. (iii) When phenacylaniline was destructively distilled at 760 mm. it gave water (37% yield, on the basis of 1 mol. from 1 mol. of phenacylaniline), aniline (35%), and a fraction of b. p. > 300° (33% by weight of original material) which, when diluted with alcohol, gave the crude triphenylpyrrole. The aniline in these decompositions was identified as its *p*-toluenesulphonyl derivative.

When a solution of diphenacyl (0·5 g.) and aniline (0·25 g., 1·2 mols.) in acetic acid (5 c.c.) was refluxed for 45 mins., the boiling solution deposited crystalline 1 : 2 : 5-triphenylpyrrole (acetic acid), m. p. 233—234°, unchanged by admixture with that obtained in the second decomposition above.

(3) *Reaction with catalysts.* The reaction with minute quantities of reagents is considered here, that with molecular quantities of primary and secondary amines under (4) and (5) respectively. Directions for one such experiment suffice for all. (*a*) A powdered mixture of pure phenacylaniline (4·2 g.) and aniline hydrobromide (0·05 g., 0·01 mol.) was placed in an oil-bath at 180° : after 1 min. a vigorous effervescence lasting 2 mins. occurred, and after 6 mins. the heating was stopped. The viscous black product, after dilution with an equal volume of hot benzene, gave on cooling 2-phenylindole (benzene), m. p. 189—190° (unchanged by admixture with authentic sample prepared by Fischer's method : cf. p. 67); yield, 1·2 g. (26%). The other catalysts producing 2-phenylindole are given in Group (a) (p. 59), and their action was always accompanied by the characteristic effervescence. The two times (in mins.) given for the following catalysts are (first) the period of heating before this effervescence started, and (second) the total time of heating : $NPhMe_2I$ (2·5; 6); pyridine methiodide (4; 20); quinoline methiodide (4; 26) and ethiodide (slight effervescence, 8; 35); quinaldine methiodide (vigorous, 6; 25) and ethiodide (vigorous, 4; 25). The times for other catalysts in Group (a) were not

materially different from those with aniline hydrobromide. (*b*) In this group the total heating lasted 7 mins. and only slight effervescence occurred. The orange-coloured product, treated as before with benzene, deposited diphenacylaniline (acetic acid or *n*-propyl alcohol), m. p. 236—238° (dependent on rate of heating); Almström (*Annalen*, 1916, **411**, 371) gives m. p. 236—240° (Found: C, 80·0; H, 6·1; N, 4·2. Calc. for $C_{22}H_{19}O_2N$: C, 80·2; H, 5·84; N, 4·2%). The catalysts $(CO_2H)_2$, NH_2Ph,HCl, and p-$C_6H_4Me{\cdot}NH_2,HCl$ yielded only diphenacylaniline, but $2NH_2Ph,(CO_2H)_2$, $2NH_2Ph,H_2SO_4$, and pyridine ethiodide yielded unchanged material in addition. (*c*) In this group there was no effervescence, and on cooling the product solidified and gave pure phenacylaniline (alcohol), m. p. 97·5—98°. (*d*) These compounds apparently caused extensive decomposition, and thick viscous syrups were obtained, from which no crystalline component could be isolated. Zinc chloride and aluminium chloride gave vigorous effervescence.

To show that the reaction described in (*a*) above was not peculiar to phenacylaniline, the following comparative experiments were performed. When pure (i) phenacyl-*o*-toluidine, or (ii) *p*-chlorophenacylaniline or (iii) *p*-chlorophenacyl-*p*-toluidine was heated at 180° for 10 mins., it was chemically unchanged; when, however, (i) or (ii) was first mixed with aniline hydrobromide (0·01 mol.), similar treatment gave the characteristic effervescence and the product yielded (i) 2-phenyl-7-methylindole (petrol), m. p. 113°, red picrate (petrol), m. p. 127·5—129° (Bischler, *loc. cit.*, gives m. p.'s 119° and 126° respectively); (ii) 2-*p*-chlorophenylindole (benzene), m. p. 205—206° (Collet, *loc. cit.*, gives m. p. 201—202°), whereas (iii), when previously mixed with *p*-toluidine hydrobromide (0·01 mol.), gave 2-p-*chlorophenyl*-5-*methylindole* (benzene), m. p. 250·5—251·5° (Found: C, 75·3; H, 5·9; N, 5·6. $C_{15}H_{12}NCl$ requires C, 74·7; H, 5·0; N, 5·8%); *nitroso*-derivative (acetic acid), orange-red powder, m. p. 277° (decomp.) (Found: N, 10·4. $C_{15}H_{11}ON_2Cl$ requires N, 10·4%). The identity of the last two indoles was confirmed by a Fischer synthesis, *p*-chloroacetophenone being condensed with phenyl- and *p*-tolyl-hydrazine respectively (p. 67).

When pure phenacylaniline was fused with zinc chloride (10 mols.) at 190° for 15 mins., and the product digested with warm hydrochloric acid, the insoluble residue on cooling formed an olive-brown solid from which no crystalline substance could be obtained. Pure *p*-chlorophenacylaniline behaved similarly. (Heating at 250° instead of 190° gave a similar result in each case.) On the other hand, acetophenacylanilide, after fusion with zinc chloride (10 mols.) at 195° for 30 mins., and aceto-*p*-chlorophenacylanilide, after similar fusion at 220° for 30 mins., followed by the above extraction, were recovered unchanged.

When diphenacylaniline was heated with aniline hydrobromide (0·01 mol.) at 240° for 7 mins., the black product did not yield any 2-phenylindole, but when it was heated with zinc dust until gentle refluxing occurred, and then further heated under reduced pressure, only a small quantity of acetophenone (semicarbazone, m. p. and mixed m. p. 199—201°) distilled. It is unlikely, therefore, that diphenacylaniline is an intermediate in the conversion of phenacylaniline into 2-phenylindole.

(4) *Reaction with primary amines.* (i) Pure phenacylaniline (5·3 g.) mixed with pure aniline (4·6 g., 2 mols.), was heated at 150° for 8 hours, and the cold product then extracted with dilute hydrochloric acid. The residual syrup crystallised when boiled with alcohol and then gave NN-*di*-(*β*-*phenylamino*-*α*-*phenylvinyl*)*aniline* (V), a white microcrystalline powder (*n*-propyl alcohol), m. p. 205—209° (dependent on rate of heating) (Found: C, 84·8; H, 5·9; N, 8·75; *M*, ebullioscopic in 1·84% acetone solution, 393; in 3·28% solution, 403; in 1·00% benzene solution, 483; in 2·11% solution, 460; cryoscopic in 0·63% ethylene dibromide solution, 506. $C_{34}H_{29}N_3$ requires C, 85·1; H, 6·1; N, 8·8%; *M*, 479·3). The use of aniline (0·5 mol.) gave the same product but less pure. (ii) When the above mixture, containing in addition aniline hydrobromide (0·01 mol.), was heated at 180° for 30 mins., and then extracted with an equal volume of boiling benzene, the solution deposited 2-phenylindole, m. p. and mixed m. p. 189°. (iii) Phenacylaniline (2·8 g.), mixed with *p*-toluidine (14 g., 10 mols.), was refluxed for 4 hours, and most of the free amine then removed by distillation. The dark residue was dissolved in benzene, extracted with dilute hydrochloric acid, dried, and the solvent removed: the residue, which slowly crystallised, was extracted with cold alcohol and then gave NN-*di*-(*β*-p-*tolylamino*-*α*-*phenylvinyl*)-p-*toluidine* (VI) (acetic acid; *n*-propyl alcohol), m. p. 175—183° (dependent on rate of heating) (Found: C, 85·5; H, 7·2; N, 7·9. $C_{37}H_{35}N_3$ requires C, 85·2; H, 6·8; N, 8·1%). (iv) A mixture of phenacylaniline, *p*-toluidine (2 mols.), and aniline hydrobromide (0·01 mol.) was heated at 180° for 7 mins., only slight effervescence occurring. The product was boiled with an equal volume of benzene and on cooling gave 2-phenyl-5-methylindole (benzene), m. p. and mixed m. p. 214—216° (Found: C, 86·9; H, 6·25; N, 6·8. Calc. for $C_{15}H_{13}N$: C, 86·9; H, 6·3; N, 6·8%). (v) Phenacylaniline was mixed with *p*-toluidine hydrobromide (1 mol.), heated at 170—180° for 6 mins., and treated as in (iv); the product required repeated crystallisation before 2-phenyl-5-methylindole, m. p. 213—214°, was isolated. The identity of this indole, obtained in (iv) and (v), was confirmed by (*a*) a Fischer synthesis from *p*-tolylhydrazine and (*b*) its conversion into the nitroso-derivative, m. p. and mixed m. p. 266—267°; Bischler (*loc. cit.*) gives m. p.'s 213° and 262° for the indole and its nitroso-derivative respectively. (vi) Phenacylaniline (4·2 g.) mixed with *o*-toluidine (4·3 g., 2 mols.) and aniline hydrobromide (0·01 mol.) was heated at 180° for 8 mins., characteristic effervescence occurring. Treatment as in (ii) gave 2-phenylindole (benzene–*cyclo*hexane), m. p. and mixed m. p. 184—188°. (vii) Repetition of (vi) but with 10 mols. of *o*-toluidine gave a product which after repeated recrystallisation (alcohol, petrol) afforded 2-phenyl-7-methylindole, m. p. and mixed m. p. 112—113°; Bischler (*loc. cit.*) gives m. p. 119°. Its identity was confirmed by conversion into the picrate (petrol), red crystals, m. p. 127·5—129°; Bischler gives m. p. 126°. (viii) Phenacylaniline (4·2 g.), mixed with 2 : 4-dimethylaniline (24·2 g., 10 mols.) and aniline hydrobromide (0·05 g., 0·01 mol.), heated at 180° for 80 mins., and then treated as in (ii), gave a viscous syrup which would not crystallise: treatment with picric acid, however, gave 2-*phenyl*-5 : 7-*dimethylindole picrate* (petrol–benzene), brown crystals, m. p. 156—157·5° (Found: C, 58·3; H, 4·1; N, 12·9. $C_{16}H_{15}N,C_6H_3O_7N_3$ requires C, 58·7; H, 4·0; N, 12·4%). (ix) Phenacyl-*p*-toluidine (4·5 g.), mixed with aniline (3·7 g., 2 mols.) and *p*-toluidine hydrobromide (0·05 g., 0·01 mol.) and heated at 180° for 7 mins., gave ultimately 2-phenyl-5-methylindole (benzene), m. p. 211—213° (mixed with authentic sample, m. p. 215—216°). (x) Repetition of (ix), but with 10 mols. of aniline, gave 2-phenylindole (alcohol), m. p. 186—187° (mixed m. p., 187·5—188·5°).

The above results explain why *p*-chlorophenacyl bromide, heated with aniline (2 mols.) at 100° for 2 mins., gave *p*-chlorophenacylaniline and the chlorophenyl ether (VIII) (cf. p. 65), but when heated with aniline (4 mols.) at 150°, for 7 hours gave 2-*p*-chlorophenylindole (65% yield); in the latter experiment, the aniline hydrobromide present would in conjunction with the longer heating at higher temperature, necessarily cause complete conversion of the phenacyl compound into the 2-arylindole.

Many attempts were made to cyclise the triamine (V) but all failed. Dry distillation gave solely aniline and benzanilide, whilst zinc chloride fusion gave an amorphous product from which no definite compound could be isolated. Heating with aniline hydrobromide (0·01 mol.) at 210° for 7 mins. caused some decomposition, but a portion of the triamine was recovered unchanged.

(5) *Reaction with secondary amines.* (i) A mixture of pure phenacylaniline (8·4 g.) and *N*-ethylaniline (24·2 g., 5 mols.) was refluxed for 4 hours, very little water being evolved. The product was dissolved in ether and then extracted in turn with dilute hydrochloric acid and water. The solution was dried (sodium sulphate), and after removal of the solvent, a dark brown oil (5·0 g.) remained, from which no crystalline substance could be isolated. (ii) On repetition of (i), but using a mixture of phenacylaniline (8·4 g.), *N*-ethylaniline (9·7 g., 2 mols.), and aniline hydrobromide (0·08 g.,

0·01 mol.), water rapidly separated as the mixture boiled. Extraction as above gave a solid residue which readily furnished 2-phenylindole (alcohol), m. p. and mixed m. p. 189—190°. (iii) A repetition of (ii), but with *N*-ethyl-*p*-toluidine (10·8 g., 2 mols.) instead of *N*-ethylaniline, gave 2-phenylindole (crude, 3·6 g., 47% of that possible on Equation 2), m. p. and mixed m. p. 187—189°. The aniline formed was isolated as *p*-toluenesulphonyl derivative (aqueous alcohol), m. p. and mixed m. p. 99—101°; yield, 1·3 g. (27% of that possible on Equation 2).

*Di-(β-phenylamino-α-*p*-chlorophenylvinyl) Ether* (VIII).—This was obtained as a by-product in the preparation of *p*-chlorophenacylaniline (p. 63), but the best yield was obtained only by using small quantities of reactants; consequently, to prepare the ether a large number of experiments using aniline (1 g.) were performed, and the products were united and worked up together. The *ether* (VIII) was obtained as bright yellow crystals, m. p. 192—193°, purified by recrystallisation from acetic acid or (rapidly) from acetic anhydride (Found: C, 70·8; H, 5·0; N, 6·2; Cl, 15·1; *M*, ebullioscopic in 0·76% acetone solution, 526; in 1·66% solution, 463. $C_{28}H_{22}ON_2Cl_2$ requires C, 71·0; H, 4·7; N, 5·9; Cl, 15·0%; *M*, 473·2). A mixture of the ether (1 g.) and acetic anhydride (10 g.), boiled for 7·5 hours, deposited on cooling colourless crystals of the *diacetyl* derivative (acetic anhydride), m. p. 232—233° after drying at 100°/15 mm. for 2 hours (Found: C, 68·8; H, 4·6; N, 5·1; Cl, 12·6. $C_{32}H_{26}O_3N_2Cl_2$ requires C, 68·9; H, 4·7; N, 5·0; Cl, 12·7%). When the ether (1 g.) was fused (i) with zinc chloride (5 g.) at 190—200° for 30 mins., extensive decomposition occurred and no definite product could be isolated; (ii) with aniline hydrobromide (0·01 mol.) at 200° for 20 mins., the ether was recovered unchanged (acetic acid), m. p. 190—192°.

Stability of 3-Phenylindole.—This indole was unchanged after being refluxed (i) with aniline (10 mols.) for 8·5 hours, (ii) with a mixture of aniline (2 mols.) and aniline hydrobromide (1 mol.) for 4 hours, (iii) with a solution of zinc chloride (4 mols.) in alcohol (18 mols.) for 5 hours. It was also unchanged when heated with aniline hydrobromide (0·01 mol.) at 200° for 10 mins. When fused with zinc chloride (7 mols.) at 250° for 0·5 hour, however, it was converted quantitatively into 2-phenylindole, m. p. and mixed m. p. 187—189°.

Secondary Amines.—The following arylalkylamines, required for phenacyl derivatives and for Fischer syntheses (p. 67), were prepared by heating the primary amine with the alkyl halide (0·45 mol.) (Hickinbottom, J., 1930, 992) to avoid tertiary amine formation, and then removing unchanged primary amine as its zinc chloride addition product (Morgan, B.P. 102843, 1916): *N*-ethylaniline; *N-iso*butylaniline, b. p. 111·5—113·5°/11·5 mm. (pure *iso*butyl bromide is required for this preparation; cf. "Organic Syntheses," 1933, **13**, 20); *N*-ethyl-*p*-toluidine, b. p. 100°/11 mm., p-*toluenesulphonyl* derivative (alcohol), colourless crystals, m. p. 71° (Found: C, 66·7; H, 7·0. $C_{16}H_{19}O_2NS$ requires C, 66·4; H, 6·6%) (cf. D.R.P. 164130); 2 : 4-*dimethyl*-N-*ethylaniline*, b. p. 229—232°/763 mm. (Found: C, 80·4; H, 10·0. $C_{10}H_{15}N$ requires C, 80·5; H, 10·1%); 2 : 4-dimethyl-*N-iso*butylaniline, b. p. 131—135°/19 mm.; p-*chloro-N-ethylaniline*, b. p. 247—250°/760 mm. (Found: N, 9·1. $C_8H_{10}NCl$ requires N, 9·0%) (cf. Hofmann, *Annalen*, 1850, **74**, 143), p-*toluenesulphonyl* derivative (alcohol), m. p. 102·5—104° (Found: C, 58·3; H, 5·3. $C_{15}H_{16}O_2NClS$ requires C, 58·1; H, 5·2%).

4-Ethoxydiphenylamine was prepared by the action of ethyl bromide on an alcoholic solution of the sodium derivative of the hydroxy-compound; colourless crystals, b. p. 196°/11 mm., m. p. 69—71°; yield, 82% (cf., Jacobson, *Ber.*, 1893, **26**, 696). 4 : 4′-*Diethoxydiphenylamine*, similarly prepared and then vacuum distilled, formed colourless crystals (alcohol), m. p. 94° (Found: C, 74·4; H, 7·4. $C_{16}H_{19}O_2N$ requires C, 74·7; 7·4%). The *p*-chlorophenacyl derivatives of these two amines appeared to undergo complete decomposition on attempted cyclisation and were not further investigated.

Phenacyl Secondary Amines.—(1) *Preparation.* The reaction of secondary amines with phenacyl halides is much less vigorous than that of primary amines. These phenacyl derivatives were therefore always prepared by boiling equimolecular quantities of the phenacyl halide and the amine in alcoholic solution with excess of calcium carbonate for 4 hours. [The use of sodium hydroxide (or even carbonate) to absorb the acid is undesirable, as the formation of cyclic "halogen-diphenacyls" may then also occur (Widman, *Ber.*, 1909, **42**, 3261; *Annalen*, 1913, **400**, 86; Almström, *Ber.*, 1914, **47**, 848).] The phenacyl secondary amine, which crystallised after filtration and cooling, was washed with water, and recrystallised (usually from alcohol). The colours of these phenacylamines, like those of the primary derivatives, varied from almost white to deep bright yellow. Phenacyl-*N*-ethylaniline, m. p. 96° (Busch and Hefele, *J. pr. Chem.*, 1911, **83**, 452, give 95°) (Found: C, 80·0; H, 7·7; N, 6·1. Calc. for $C_{16}H_{17}ON$: C, 80·3; H, 7·2; N, 5·9%), has considerable stability; when subjected to steam distillation for 3 hours, a small portion volatilised and the remainder was unchanged: *hydrochloride*, obtained by passing hydrogen chloride into a benzene solution of the amine, colourless crystals, m. p. 158° (Found: N, 5·3. $C_{16}H_{17}ON,HCl$ requires N, 5·1%); *picrate*, deep red crystals (alcohol) becoming yellow when powdered, m. p. 110° (Found: C, 56·7; H, 4·5. $C_{16}H_{17}ON,C_6H_3O_7N_3$ requires C, 56·3; H, 4·6%).

*Phenacyl-*N*-ethyl-*p*-toluidine* (alcohol), m. p. 110—111° (Found: N, 5·7. $C_{17}H_{19}ON$ requires N, 5·5%). p-*Chlorophenacyl-N-methylaniline* (alcohol), m. p. 109·5—110° (Found: C, 69·3; H, 5·5. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·5%). p-*Chlorophenacyl-N-ethylaniline* (alcohol), m. p. 83° (Found: C, 70·2; H, 5·7; N, 5·2. $C_{16}H_{16}ONCl$ requires C, 70·2; H, 5·85; N, 5·1%); *hydrochloride*, m. p. 169° (Found: N, 4·3. $C_{16}H_{16}ONCl,HCl$ requires N, 4·5%); *picrate*, dark yellow crystals (alcohol), m. p. 116—117° (Found: C, 52·8; H, 4·0. $C_{16}H_{16}ONCl,C_6H_3O_7N_3$ requires C, 52·5; H, 3·8%). p-*Chlorophenacyl-*N*-isobutylaniline* (alcohol), m. p. 91° (Found: N, 4·8. $C_{18}H_{18}ONCl$ requires N, 4·6%). p-*Chlorophenacyl-*N*-ethyl-*p*-toluidine*, yellow needles (alcohol), m. p. 95·5° (Found: C, 70·3; H, 6·1; N, 4·8; *M*, ebullioscopically in 1·12% acetone solution, 273; in 2·20% solution, 248. $C_{17}H_{18}ONCl$ requires C, 70·9; H, 6·3; N, 4·9%; *M*, 287·7); *hydrochloride* (dilute hydrochloric acid), m. p. 177—178° (decomp.) (Found: C, 63·0; H, 5·6. $C_{17}H_{18}ONCl,HCl$ requires C, 63·0; H, 5·9%); *picrate*, yellow crystals (alcohol), m. p. 135—136° (Found: C, 53·2; H, 4·3. $C_{17}H_{18}ONCl,C_6H_3O_7N_3$ requires C, 53·4; H, 4·1%). The pure base is stable at room temperature for several months, whereas crude samples decompose rapidly to a brown viscous syrup. p-*Chloro-*(p′-*chlorophenacyl*)-N-*ethylaniline*, colourless needles (alcohol), m. p. 105—106° (Found: C, 62·6; H, 5·1. $C_{16}H_{15}ONCl_2$ requires C, 62·3; H, 4·9%).

(2) *Reactions with zinc chloride, etc.* (A) (i) When a mixture of phenacyl-*N*-methylaniline (5 g.), powdered zinc chloride (10 g., 4 mols.), and alcohol (22 c.c.) was refluxed for 4 hours, filtered, and set aside, the unchanged phenacyl compound (1·5 g., m. p. 119—120°) crystallised on cooling. On longer standing, crystals of 3-phenyl-1-methylindole (alcohol), m. p. 66°, separated (Found: C, 86·95; H, 6·45; N, 6·9. Calc. for $C_{15}H_{13}N$: C, 86·9; H, 6·3; N, 6·8%); picrate, chocolate-brown crystals (alcohol), m. p. 91—92° (Found: N, 12·9. Calc. for $C_{15}H_{13}N,C_6H_3O_7N_3$: N, 12·8%). Ince (*Annalen*, 1889, **253**, 37) gives m. p.'s 64—65° and 90° respectively.

When a mixture of phenacyl bromide (13 g.) and pure *N*-methylaniline (14 g., 2 mols.) was refluxed, a vigorous reaction occurred; after 1 hour, the product was extracted with hydrochloric acid, and the residue dried and distilled; 3-phenyl-1-methylindole (7·0 g., 52% of theoretical), b. p. 205—215°/12 mm., m. p. 65—66° (alcohol, petrol) was again obtained: picrate, m. p. and mixed m. p. 89—91°. (The use of phenacyl chloride gave a similar result.) This refutes Culmann's statement (*loc. cit.*) that phenacyl bromide and *N*-methylaniline react to give 2-phenylindole, a result which must have been due to the presence of aniline as an impurity in the base.

(ii) When the mixture in (i), but without the alcohol, was heated under reflux at 250° for 40 mins., and the product extracted with hydrochloric acid, the residue gave colourless needles of 2-phenyl-1-methylindole (acetic acid), m. p.

100—100·5° (Found: C, 86·9; H, 6·6; N, 6·8. Calc. for $C_{15}H_{13}N$: C, 86·9; H, 6·3; N, 6·8%); Degen (*Annalen*, 1886, **236**, 155) gives m. p. 100—101°. The indole was characterised as its green 3-nitroso-derivative (alcohol), m. p. 143° (Found: N, 11·4. Calc. for $C_{15}H_{12}ON_2$: N, 11·9%): Campbell and Cooper (*loc. cit.*) give m. p. 144°.

When a mixture of 3-phenyl-1-methylindole (2 g.) and powdered zinc chloride (10 g.) was heated with stirring at 250° for 30 mins., and the product then extracted with warm dilute hydrochloric acid, the insoluble residue became semi-solid on cooling, and, after two recrystallisations from acetic acid, gave pure 2-phenyl-1-methylindole (0·9 g.), m. p. and mixed m. p. 100—101°.

(B) Phenacyl-*N*-ethylaniline in alcoholic solution, when refluxed with zinc chloride (1 mol.) for 4 hours, was unchanged. When similarly refluxed with zinc chloride (4 mols.), or when fused with anhydrous zinc chloride (10 mols.) at 250° for 40 mins., extraction as in (A) (i) or (ii) gave 3-*phenyl*-1-*ethylindole* as a pale yellow oil, b. p. 188—192°/1·5 mm., which did not crystallise (Found: C, 86·4; H, 7·0; N, 6·5. $C_{16}H_{15}N$ requires C, 86·8; H, 6·8; N, 6·3%): *picrate*, dark brown needles from saturated alcoholic picric acid, m. p. 83—83·5° (Found: C, 60·0; H, 4·3; N, 12·4. $C_{16}H_{15}N,C_6H_3O_7N_3$ requires C, 60·0; H, 4·0; N, 12·5%); the picrate slowly decomposes in hot alcohol. A nitroso-compound could not be obtained from the indole. Note: 2-phenyl-1-ethylindole has m. p. 84—84·5° (Fischer, *loc. cit.*), readily gives a green nitroso-compound (see later), and does not form a picrate under the above conditions.

(C) Phenacyl-*N*-ethyl-*p*-toluidine was also unaffected by boiling with zinc chloride (1 mol.) in alcohol, but with zinc chloride (4 mols.) in alcohol (4 hours), or with anhydrous zinc chloride (10 mols.) at 250° for 30 minutes, gave liquid 3-*phenyl*-5-*methyl*-1-*ethylindole*, b. p. 220—222°/17 mm., which did not crystallise (Found: C, 86·6; H, 7·0; N, 5·85. $C_{17}H_{17}N$ requires C, 86·8; H, 7·2; N, 6·0%). It did not give a green nitroso-derivative, but gave a *picrate* (alcohol), dark brown needles, m. p. 107·5—108° (Found: C, 59·6; H, 4·4; N, 12·0. $C_{17}H_{17}N,C_6H_3O_7N_3$ requires C, 59·5; H, 4·35; N, 12·1%).

(D) *p*-Chlorophenacyl-*N*-methylaniline, with alcoholic zinc chloride (4 mols.) or anhydrous zinc chloride (10 mols.), as in (C), gave 3-p-*chlorophenyl*-1-*methylindole* (acetic acid), m. p. 96° (Found: C, 74·1; H, 5·1; N, 6·0; Cl, 14·5. $C_{15}H_{12}NCl$ requires C, 74·5; H, 5·0; N, 5·8; Cl, 14·7%): *picrate* (alcohol), dark brown crystals, m. p. 107—107·5° (Found: C, 53·8; H, 3·3; N, 11·9; Cl, 7·8. $C_{15}H_{12}NCl,C_6H_3O_7N_3$ requires C, 53·6; H, 3·2; N, 11·9; Cl, 7·5%). The pure indole, when fused with anhydrous zinc chloride (10 mols.) at 250°, was, as expected, unchanged.

When a mixture of *p*-chlorophenacyl bromide and *N*-methylaniline (2 mols.) was refluxed, a vigorous reaction occurred, and the product yielded the above indole, m. p. and mixed m. p. 94—95·5°, giving a picrate, m. p. and mixed m. p. 107°.

(E) *p*-Chlorophenacyl-*N*-ethylaniline, fused with zinc chloride (8 mols.) at 250° for 0·5 hour, gave 3-p-*chlorophenyl*-1-*ethylindole* (alcohol), m. p. 81°, b. p. 168°/0·1 mm. (Found: C, 75·0; H, 5·75. $C_{16}H_{14}NCl$ requires C, 75·15; H, 5·5%).

(F) *p*-Chlorophenacyl-*N*-*iso*butylaniline, treated as in (E), gave 3-p-*chlorophenyl*-1-iso*butylindole* (alcohol), m. p. 71—72°, b. p. 245°/15 mm. (Found: C, 76·25; H, 6·3. $C_{18}H_{18}NCl$ requires C, 76·2; H, 6·4%).

(G) *p*-Chlorophenacyl-*N*-ethyl-*p*-toluidine (i) when heated in an open dish at 100° for 7 hours yielded much unchanged material and also a small quantity of *p*-chlorobenzoic acid, m. p. and mixed m. p. 238° (Found: C, 53·7; H, 3·6; Cl, 21·9. Calc.: C, 53·7; H, 3·2; Cl, 22·7%). (ii) When mixed with powdered anhydrous sodium acetate (3 mols.) and heated in an open dish at 145° for 8·5 hours was unchanged and did not contain *p*-chlorobenzoic acid. (iii) When refluxed with tetralin (b. p. 206°) for 3 hours gave water and a small quantity of unchanged material; distillation removed the solvent and then gave 3-p-*chlorophenyl*-5-*methyl*-1-*ethylindole* (alcohol, acetic acid), m. p. 92° (Found: C, 75·3; H, 5·73; N, 5·2. $C_{17}H_{16}NCl$ requires C, 75·7; H, 5·9; N, 5·2%): *picrate* (alcohol) dark brown needles, m. p. 102·5—103·5° (Found: N, 11·5. $C_{17}H_{16}NCl,C_6H_3O_7N_3$ requires N, 11·2%); the tetralin distillate slowly deposited *p*-chlorobenzoic acid, m. p. and mixed m. p. 239—240°. (iv) When refluxed with alcoholic zinc chloride (1 mol.) for 4 hours, gave on cooling much unchanged material; the filtrate, set aside overnight, deposited bright yellow crystals of the *dimer* (acetone–alcohol), m. p. 157·5° (Found: C, 71·1; H, 6·2; N, 5·0; Cl, 12·2; *M*, ebullioscopic in 0·33% acetone solution, 564; in 0·63% solution, 534. $C_{34}H_{36}O_2N_2Cl_2$ requires C, 70·9; H, 6·3; N, 4·9; Cl, 12·4%; *M*, 575·4). For crystallographic data, see p. 68. (v) When refluxed with alcoholic zinc chloride (4 mols.) for 4 hours, gave, after filtration and cooling, the above indole, m. p. and mixed m. p. 91—92°. (vi) When fused with zinc chloride (10 mols.) at 250° for 30 mins. also gave this indole.

The preparation of the above 3-aryl-1-alkylindoles (B—G) was also performed in one operation by heating a mixture of the secondary amine, phenacyl bromide, chlorobenzene, zinc oxide, and zinc chloride in an autoclave at 190° for 6 hours, as stated in B.P. 496657.

It is clear from the above results that 3-aryl-1-alkylindoles, with the exception of the phenylmethyl member, are not isomerised by fusion with zinc chloride. This was confirmed by (i) fusing 3-*p*-chlorophenyl-1-ethylindole (10 g.) with zinc chloride (50 g.) for 0·5 hour at 250°; (ii) heating this indole (10 g.) with zinc chloride (10 g.) and concentrated hydrochloric acid (20 c.c.) in a sealed tube at 190° for 18 hours; (iii) heating the indole (10 g.) with zinc chloride (25 g.) and chlorobenzene (50 c.c., previously saturated with hydrogen chloride) in a sealed tube at 170° for 8 hours. In all three cases, the indole was recovered unchanged, contrary to the statements in B.P. 496657.

(3) *Reactions with primary amines.* (A) (i) A mixture of phenacyl-*N*-ethylaniline (12 g.) and aniline (7·0 g., 1·5 mols.) was heated at 150° for 8 hours, and the free amines, removed by steam-distillation, gave *p*-toluenesulphonanilide (1 g.), m. p. 101°, and *p*-toluenesulphonethylanilide (4·1 g.), m. p. 86·5—87°: these correspond to aniline (0·6 g., 12% recovery of amine used) and *N*-ethylaniline (2·9 g., 48% of that present originally as phenacylamine). The dark brown residue from the distillation solidified on cooling (9·3 g.) and was pulverised, thrice extracted with boiling alcohol, and then recrystallised (acetic acid, *n*-propyl alcohol), the triamine (V), m. p. 206—209° (shrinking at 195°), being thus obtained (Found: C, 85·2; H, 6·0; N, 9·0%). The three united alcoholic extracts, which smelt strongly of phenyl *iso*cyanide, gave on cooling a second crop of (V); this was removed, the alcohol evaporated, and the residue distilled, benzanilide, b. p. 210—220°/25 mm., m. p. and mixed m. p. 161—163°, being thus obtained (Found: C, 79·1; H, 5·7; N, 7·0. Calc.: C, 79·1; H, 5·6; N, 7·1%).

(ii) Repetition of (i), but with *p*-chloroaniline (9·6 g., 1·5 mols.) instead of aniline, gave on steam-distillation mixed amines (6·7 g.) which furnished *p*-toluenesulphon-ethylanilide (4·0 g.) and -*p*-chloroanilide (1·4 g.); the latter, after one and two crystallisations from aqueous alcohol, had m. p. 91—94° and 120—121° respectively (Found: C, 55·2; H, 4·65. Calc. for $C_{13}H_{12}O_2NClS$: C, 55·4; H, 4·3%). Since Chattaway (J., 1904, **85**, 1184) gives m. p. 95° and D.R.-P. 164130 gives m. p. 119°, the compound is clearly dimorphous. The residue from the steam-distillation could not be purified, but the experiment proves the interchange of amines.

(B) When a mixture of phenacyl-*N*-ethyl-*p*-toluidine (12·8 g.) and aniline (7 g., 1·5 mols.) was treated as in (A) (i), steam-distillation gave aniline and *N*-ethyl-*p*-toluidine (identified as *p*-toluenesulphonyl derivatives, 1·0 g., m. p. 100—101°, and 4·1 g., m. p. 71—71·5°, respectively) and a strong odour of phenyl *iso*cyanide. The residue, purified as before, gave the triamine (V) (acetic acid, *n*-propyl alcohol), m. p. 200—205°, softening at 195° (m. p. 200—210° mixed with authentic sample) (Found: C, 85·4; H, 5·8; N, 8·9%).

(C) (i) A mixture of *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine (10·3 g.) and aniline (4·9 g., 1·5 mols.) treated as in (A) (i), gave mixed bases (2·1 g.), proved as above to be aniline and ethyl-*p*-toluidine; the residue gave *NN-di*-(*β-phenylamino*-*α*-p-*chlorophenylvinyl*)*aniline* (VII) (acetic acid, *n*-propyl alcohol) as a buff-coloured, microcrystalline powder, m. p.

172—180° dependent on rate of heating (Found: C, 74·6; H, 5·1; N, 6·9; Cl, 13·45; *M*, cryoscopic in 0·92% ethylene dibromide solution, 512. $C_{24}H_{17}N_3Cl_2$ requires C, 74·4; H, 5·0; N, 7·65; Cl, 12·9%; *M*, 548·3). (ii) The same mixture, heated as before and then extracted with alcohol, gave ultimately the *p*-chloro-ether (VIII), m. p. 191·5—192°, thus proving the intermediate formation of *p*-chlorophenacylaniline. (iii) A mixture of the phenacylamine with aniline (4 mols.), refluxed for 6·5 hours, gave a solid product contaminated with *N*-ethyl-*p*-toluidine; this solid on recrystallisation gave *p*-chlorobenzanilide (alcohol), m. p. and mixed m. p. 199—200° (Found: C, 67·6; H, 4·5; N, 6·1; Cl, 15·4. Calc.: C, 67·4; H, 4·35; N, 6·05; Cl, 15·3%).

(4) *Reactions with secondary amines.* (A) (i) A mixture of *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine (10 g.) and *N*-ethyl-*p*-toluidine (4·7 g., 1 mol.) was heated in an open basin at 100° for 7 hours, during which crystals formed around the melt. The cold, almost solid product, dissolved in hot alcohol, deposited 4 : 4′-dichlorobenzil (alcohol), 0·8 g., m. p. 199° (Found: C, 60·2; H, 3·0; Cl, 25·8. Calc. for $C_{14}H_8O_2Cl_2$: C, 60·2; H, 2·9; Cl, 25·4%), unchanged by admixture with an authentic sample prepared by Gomberg and Natta's method (*J. Amer. Chem. Soc.*, 1929, **51**, 2241): The alcoholic mother-liquors slowly deposited 2·0 g. of *p*-chlorobenzoic acid (alcohol), m. p. and mixed m. p. 238°.

(ii) The above mixture was heated in a loosely-plugged flask at 140—150° for 7 hours, and the product then mixed with acetic acid (40 c.c.); the residual crystals were *p*-chlorobenzoic acid (alcohol), m. p. and mixed m. p. 238°; yield 0·5 g. The acetic acid liquor, when set aside, slowly deposited *p-chloro-*(*αβ-bis-*p*-tolylethylamino)vinylbenzene* (IX) (alcohol), colourless needles, m. p. 123—123·5° (Found: C, 77·0; H, 6·9; N, 7·1; Cl, 9·0; *M*, cryoscopic in 0·62% ethylene dibromide solution, 396; in 1·15% solution, 398; ebullioscopic in 1·75% acetone solution, 388; in 3·06% solution, 376. $C_{28}H_{29}N_2Cl$ requires C, 77·1; H, 7·2; N, 6·9; Cl, 8·8%; *M*, 404·8); yield, 0·7 g.

As an alternative treatment, a solution of the above crude reaction product in ether (100 c.c.) was extracted in turn with dilute sodium hydroxide solution, dilute hydrochloric acid, and water, dried (sodium sulphate), the solvent removed, and the residue distilled. A dark red, viscous fraction, b. p. 140—240°/0·1 mm., was dissolved in hot acetic acid, and slowly deposited 0·1 g. of the above diamine (IX), m. p. and mixed m. p. 119—120°. On one occasion, a repetition of this experiment gave a viscous distillate, b. p. 100—220°/0·1 mm., which, however, furnished 4 : 4′-dichlorobenzil (alcohol–acetone) (0·05 g.), m. p. and mixed m. p. 198°.

The diamine (IX) was recovered unchanged after it had been (*a*) refluxed at 760 mm. for 5 mins., (*b*) heated with zinc oxide at 140—150° for 7 hours, with zinc chloride at 220° for 0·5 hour, or with alcoholic hydrogen chloride at 120—125° for 32 hours, (*c*) boiled with concentrated hydrochloric acid for 2·5 hours, (*d*) dissolved in excess methyl iodide at room temperature for 3 days, (*e*) dissolved in alcoholic picric acid for 1 week, (*f*) shaken in acetic acid solution with hydrogen and Adams's platinum oxide catalyst, and (*g*) similarly treated in the presence of a palladium–charcoal catalyst.

(iii) When the above mixture, (A) (i), contained powdered anhydrous sodium acetate (3 mols.), heating at 140—150° for 10 hours gave small quantities of *p*-chlorobenzoic acid and dichlorobenzil, much unchanged phenacyl compound, but no diamine. (iv) When experiment (ii) was repeated in a carbon dioxide or a hydrogen atmosphere, the mixture was unchanged; the production of the acid and the diketone is therefore due to atmospheric oxidation.

(v) When the phenacylamine (9·6 g.) was heated with 2 : 4-dimethyl-*N*-ethylaniline (5 g., 1 mol.) at 140—150° for 7 hours, *p*-chlorobenzoic acid (1·7 g., 32% of theoretical) and 4 : 4-dichlorobenzil (*ca.* 0·2 g.) were isolated; repetition, but with *N-iso*butylaniline (5·2 g., 1 mol.), gave the acid but no diketone.

(vi) When the phenacylamine (2·5 g.) and *N*-ethylaniline (4·5 g., 4 mols.) were refluxed together for 3·5 hours, and the product extracted with dilute hydrochloric acid, the insoluble residue furnished 3-*p*-chlorophenyl-5-methyl-1-ethyl indole (alcohol), m. p. and mixed m. p. 90·5—91°. Repetition, but with replacement of the *N*-ethylaniline by *N-iso*-butylaniline (5·2 g., 4 mols.) or *N*-ethyl-*p*-toluidine (4·7 g., 4 mols.), gave the same result.

(B) When mixtures of *p*-chlorophenacyl-*N*-ethylaniline (2·7 g.) and *N*-ethylaniline (4·8 g., 4 mols.), or *N-iso*butylaniline (6·0 g., 4 mols.) or *N*-ethyl-*p*-toluidine (5·4 g., 4 mols.) were refluxed for 5 hours, treatment as in (A) (vi) gave always 3-*p*-chlorophenyl-1-ethylindole (alcohol; acetic acid), m. p.'s (in the 3 experiments) 80°, 79°, 74—75°, undepressed by admixture with an authentic sample.

Syntheses by Fischer's Method.—(a) *Secondary amines* (see p. 65). (b) *Nitrosoamines.* These were prepared by usual methods; p-*chlorophenyl-N-ethylnitrosoamine* (alcohol), colourless needles, m. p. 58—59° (Found: N, 15·3. $C_8H_9ON_2Cl$ requires N, 15·2%). (c) *Hydrazines.* (i) Monoarylhydrazines were prepared by reducing the diazo-salts with sodium sulphite and sulphur dioxide, better yields being thus obtained than by Thomson's hydrosulphite method (*J. Soc. Dyers Col.*, 1921, **37**, 7). (ii) *as.*-Arylalkylhydrazines were prepared by (*a*) reduction of the nitrosoamine, or (*b*) through the sodium derivative of the monoarylhydrazine (p. 63).

The following directions illustrate method (*b*). Sodamide (42 g.) was pulverised under benzene, the mixture transferred to a flask, the total benzene made up to 250 c.c., warmed under reflux, and phenylhydrazine (108 g.) added. Yellow needles separated, and after 1·5 hours' boiling, the mixture was allowed to cool, ethyl bromide (110 g., 1 mol.) added, and, when the vigorous reaction had subsided, refluxing was continued for another hour. The mixture was filtered, and the benzene distilled; the residual oil was dissolved in chloroform (500 c.c.), and dry hydrogen chloride passed in to precipitate unchanged phenylhydrazine as its hydrochloride, which was collected. The chloroform filtrate was then shaken in turn with aqueous sodium hydroxide and water, dried (sodium sulphate), the solvent removed, and the free phenylethylhydrazine distilled; b. p. 133°/19 mm.; yield, 67 g. (50%). The following b. p.'s were recorded: phenyl-*n*-propylhydrazine, 137°/25 mm.; phenyl*iso*butylhydrazine, 140°/22 mm. (acetyl derivative, m. p. 115—116°); *p*-tolylethylhydrazine, 122—124°/12 mm. (cf. Hegel, *Annalen*, 1886, **232**, 214; Michaelis *et al.*, *ibid.*, 1889, **252**, 270; *Ber.*, 1897, **30**, 2815).

(d) *Hydrazones.* These were seldom isolated [see (e) below]. p-*Chloroacetophenonephenylhydrazone* (alcohol), m. p. 112—113° (Found: N, 11·8. $C_{14}H_{13}N_2Cl$ requires N, 11·5%).

(e) *Indoles.* Fischer (*Annalen*, 1886, **236**, 133) and Fischer and Schmidt (*loc. cit.*) have shown that acetophenonephenylhydrazone on fusion with zinc chloride gives 2-phenylindole, m. p. 186°, but that phenylacetaldehydephenylhydrazone when boiled with alcoholic hydrogen chloride gives 3-phenylindole, m. p. 89°, and when fused with zinc chloride gives 2-phenylindole, isomerisation occurring in the last case. We have confirmed the formation of 3-arylindoles by the use of alcoholic hydrogen chloride. For the preparation of authentic 2-aryl-1-alkylindoles, however, we have employed zinc chloride, without isolating the intermediate hydrazone. The general method consisted in heating a mixture of the *as.*-arylalkylhydrazine, acetophenone (or the *p*-chloro-derivative), and excess of zinc chloride at *ca.* 200° for 10—15 mins.; the product was poured into hot dilute hydrochloric acid, and the liberated indole extracted with benzene, dried, distilled when necessary, and crystallised. For the preparation of the 3-nitroso-2-aryl-1-alkylindoles, sodium nitrite (2 mols.) was added to a cold solution of the indole in acetic acid; after several hours, the solution was slowly diluted with water; the green nitroso-compound crystallised on stirring. 2-*Phenyl*-1-*ethylindole* (alcohol, acetic acid), b. p. 207—209°/19 mm., m. p. 84—84·5° (Found: C, 87·0; H, 7·0; N, 6·4. $C_{16}H_{15}N$ requires C, 86·8; H, 6·85; N, 6·35%) (cf. Baeyer and Co., D.R.-P. 128660); 3-*nitroso*-derivative, m. p. 130—131° (Found: N, 11·5. $C_{16}H_{14}ON_2$ requires N, 11·2%). 2-*Phenyl*-5-*methyl*-1-*ethylindole*, b. p. 171—173°/0·2 mm., m. p. 70·5° (Found: C, 86·6; H, 7·0; N, 6·5. $C_{17}H_{17}N$ requires C, 86·8; H, 7·2; N, 6·0%) (Baeyer and Co., *ibid.*); 3-*nitroso*-derivative, m. p. 161—162° (Found: C, 76·8; H, 6·4; N, 10·8. $C_{17}H_{16}ON_2$ requires C, 77·3; H, 6·1; N, 10·6%). 2-p-*Chlorophenyl*-1-*ethylindole*, b. p. 171°/0·2 mm.,

m. p. 86—87° (Found: C, 74·9; H, 5·8. $C_{16}H_{14}NCl$ requires C, 75·15; H, 5·5%); 3-*nitroso*-derivative, m. p. 138—139° (Found: C, 67·3; H, 4·9. $C_{16}H_{13}ON_2Cl$ requires C, 67·5; H, 4·6%). 2-p-*Chlorophenyl*-1-n-*propylindole*, b. p. 222—225°/15 mm., m. p. 54° (Found: C, 76·2; H, 6·2; N, 5·0. $C_{17}H_{16}NCl$ requires C, 75·7; H, 5·9; N, 5·1%); 3-*nitroso*-derivative, m. p. 137—138° (Found: C, 68·0; H, 5·1; N, 9·7. $C_{17}H_{15}ON_2Cl$ requires C, 68·3; H, 5·1; N, 9·4%). 2-p-*Chlorophenyl*-1-iso*butylindole*, b. p. 173—178°/0·3 mm., 230—232°/13 mm., m. p. 87—87·5° (Found: C, 76·5; H, 6·0; N, 4·8. $C_{18}H_{18}NCl$ requires C, 76·5; H, 6·3; N, 4·9%); 3-*nitroso*-derivative, m. p. 93° (Found: N, 9·0. $C_{16}H_{17}ON_2Cl$ requires N, 9·0%). 2-p-*Chlorophenyl*-5-*methyl*-1-*ethylindole*, b. p. 239°/13 mm., m. p. 127—128·5° (Found: C, 75·9; H, 6·0; N, 5·2; Cl, 13·3. $C_{17}H_{16}NCl$ requires C, 75·7; H, 5·9; N, 5·1; Cl, 13·2%). All the above indoles were colourless and their 3-nitroso-derivatives deep green. The indoles were usually crystallised from alcohol or acetic acid, and their nitroso-derivatives from alcohol or light petroleum.

Drs. Hargreaves and Taylor report on the dimeric polymeride obtained from *p*-chlorophenacyl-*N*-ethyl-*p*-toluidine: "*Physical and Optical Properties.*—The material recrystallises from acetone in the form of large thick yellow plates. The shape of the plate face is usually that of a parallelogram. Slight pleochroism is observed when plane polarised light is transmitted through the plate face, maximum and minimum absorption occurring for directions of variation of the light which are inclined to the edges of the parallelogram. Examination between crossed Nicols with the light transmitted normally through the plate face reveals that the extinction direction is also inclined to the side of the parallelogram.

In some crystals, faces are developed at right angles to the plate face. When light is passed normally through these faces, and between crossed Nicols, extinction occurs parallel and perpendicular to the edges lying in the plate face.

The density of the crystals, measured by flotation in an aqueous solution of strontium bromide, is 1·24.

X-ray Data. X-ray rotation, oscillation, and Weissenberg photographs reveal that the crystals are monoclinic, with the symmetry axis normal to the plate face. This is in agreement with the observations on extinction directions.

The unit cell dimensions are: $a = 9·7$ A., $b = 18·1_3$ A., $c = 10·35$ A., $\beta = 57°$.

The density of the crystals, calculated from the contents and dimensions of the unit cell, is

$$\Delta = \frac{1·65 \times 575 \times \text{No. mols. per unit cell}}{18·1_3 \times 9·7 \times 10·35 \times 0·839} = 0·62_1 \times \text{No. mols. per unit cell.}$$

With two mols. in the unit cell the calculated density is $1·24_2$, in agreement with the observed density of 1·24.

Indexing of the oscillation and Weissenberg photographs indicates that all reflections of type {*hkl*} are present, reflections {*h*0*l*} are present only when *h* is even, and reflections {0*k*0} are present only when *k* is even. The {*h*0*l*} halving has been firmly established by examination of the {*h*0*l*} reflections recorded on a zero-layer line Weissenberg photograph taken with the crystal rotating about the asymmetry axis. The {0*k*0} halving is based on the absence of all odd orders of {0*k*0} up to $k = 17$.

The space group is therefore $C_{2h}^5 - P_{2_1}/a$.

There are 4 equivalent general positions per unit cell in a lattice with the space group P_{2_1}/a, and it is only possible to have 2 molecules per unit cell if the molecules are centro-symmetrical and lie with their symmetry centres on symmetry centres in the space lattice. As the unit cell of the material under investigation has been found to contain only 2 molecules, it is clear that these molecules must therefore be centro-symmetrical."

We are indebted to Mr. F. G. Holliman, B.A., for some assistance in the experimental work, to St. Catharine's College and to Messrs. I.C.I. (Dyestuffs) Ltd., for grants, and to the latter also for materials.

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22. *The Action of Phosphorus Pentachloride on Non-symmetrically Substituted Acetones.*

By AHMAD ZAKI and YOUSSEF ISKANDER.

The action of phosphorus pentachloride on boiling benzene solutions of the five ketones mentioned below gave equilibrium mixtures of chloro-olefins. The reactivity of the chlorine atom, as tested by sodium ethoxide, was increased by the presence of nitro-groups: the mononitro-compound gave a mixture of the corresponding ethyl ether and acetylenic compound by boiling, whereas the dinitro-compound gave only the acetylenic compound and in the cold.

Attempts to prepare a non-symmetrically substituted acetone from *ethyl* α-2 : 4-*dinitrophenyl*-γ-*phenylaceto-acetate* led to the formation of substituted naphthalenes.

KETONES, $Ar·CH_2·CO·CH_2R$ [Ar = Ph and R = H, Me, or Et; or R = H and Ar = p-$C_6H_4·NO_2$ or 2 : 4-$C_6H_3(NO_2)_2$], react with phosphorus pentachloride in boiling benzene with evolution of hydrogen chloride and formation of chloro-olefins, $Ar·CH{:}CCl·CH_2R$ and $Ar·CH_2·CCl{:}CHR$. These were separated by fractional distillation or in suitable cases by crystallisation. Their structures were determined by ozonolysis in chloroform, $Ar·CH{:}CCl·CH_2R$ giving Ar·CHO and $R·CH_2·COCl$, and $Ar·CH_2·CCl{:}CHR$ giving $Ar·CH_2·COCl$ and R·CHO. These products were difficult to separate, so the ozonolysis was effected in alcohol–chloroform, giving separable mixtures of esters, aldehydes, and acids, the last produced by partial oxidation of the aldehydes.

The two chloro-olefinic isomers obtained by distillation were individual substances, but changed in course of time into the same equilibrium mixture, the components of which were either separated by distillation or identified by ozonolysis.

The chlorine atom in the chloro-olefins showed fair stability towards boiling alcoholic sodium ethoxide, except in the case of the mononitro-compounds, which were readily converted into β-*ethoxy*-α-p-*nitrophenyl*-Δ^{α}-*propylene* and α-p-*nitrophenylallylene*, and in the case of β-*chloro*-α-2 : 4-*dinitrophenyl*-Δ^{α}-*propylene*, which gave only α-2 : 4-*dinitrophenylallylene* with cold sodium ethoxide solution.

Methods of Synthesis.—*p*-Nitrobenzyl methyl ketone, first obtained as a by-product of the action of diazomethane on *p*-nitrophenylacetaldehyde (*Ber.*, 1929, **62**, 51), has been prepared in 20% yield by West and Soliman

of the Egyptian University (private information) by the action of *p*-nitrophenylacetyl chloride on acetoacetic ester (sodio-derivative) in dry benzene, hydrolysis of the resulting α-*p*-nitrophenylacetylacetoacetic ester with dilute aqueous ammonia at 40°, and hydrolysis of the product, γ-*p*-nitrophenylacetoacetic ester, with dilute sulphuric acid. By substituting malonic ester for acetoacetic ester, we have increased the yield to 40%.

In an attempt to prepare 2 : 4-dinitrodibenzyl ketone *ethyl* α-2 : 4-*dinitrophenyl*-γ-*phenylacetoacetate* was prepared by the action of ethyl γ-phenylacetoacetate (sodio-derivative) on 1-chloro-2 : 4-dinitrobenzene in absolute alcohol. The product was resinified by concentrated sulphuric acid and unchanged by dilute sulphuric or hydrochloric acid; boiling with 5% sodium hydroxide solution produced 1 : 3-*dihydroxy*-2-2′ : 4′-*dinitrophenylnaphthalene*. When the ester was boiled with the equivalent amount of alcoholic sodium ethoxide, 3-*hydroxy*-1-*ethoxy*-2-2′ : 4′-*dinitrophenylnaphthalene* was formed, hydrolysis of which by boiling dilute alkali gave the preceding 1 : 3-dihydroxy-derivative.

Experimental.

Ethyl p-*Nitrophenylacetylmalonate*.—Sodium (23 g.; 1 mol.) in absolute alcohol (500 c.c.) and *p*-nitrophenylacetyl chloride (99·5 g.; 0·5 mol.) in dry benzene (400 c.c.) were successively added during 4 hours to ethyl malonate (80 g.; 0·5 mol.) in absolute alcohol (375 c.c.), cooled in a freezing mixture. The mixture was then stirred for 1 hour longer and kept in the ice-chest overnight. The precipitated sodio-derivative was acidified, and the liberated oil extracted with ether and washed with sodium bicarbonate solution (yield, 65 g.). It was converted, by addition to the required amount of sodium ethoxide in absolute alcohol, into the *sodio*-derivative of ethyl *p*-nitrophenylacetylmalonate, which separated from absolute alcohol in yellowish microcrystalline cubes (Found: C, 48·9; H, 4·6; N, 4·3; Na, 6·6. $C_{15}H_{16}O_7NNa$ requires C, 48·7; H, 4·7; N, 4·1; Na, 6·7%).

p-Nitrobenzyl methyl ketone, prepared from ethyl *p*-nitrophenylacetylmalonate by means of hydrochloric acid (*d* 1·1), crystallised from light petroleum (b. p. 70—80°) in scales, m. p. 65°, not depressed by an authentic specimen. Yield, 40%.

p-*Nitrophenylacetic anhydride*, prepared from *p*-nitrophenylacetyl chloride and sodium *p*-nitrophenylacetate in boiling benzene and crystallised from acetone, had m. p. 153° (Found: C, 55·7; H, 3·6; N, 8·1. $C_{16}H_{12}O_7N_2$ requires C, 55·8; H, 3·5; N, 8·1%).

Ethyl α-2 : 4-*Dinitrophenyl*-γ-*phenylacetoacetate*.—Ethyl γ-phenylacetoacetate (31 g.; 2 mols.) (Sonn and Litten, *Ber.*, 1933, **66**, 1512) was treated with sodium (3·46 g.; 2 mols.) in absolute alcohol (400 c.c.), and 1-chloro-2 : 4-dinitrobenzene (15·25 g.; 1 mol.) in ether (100 c.c.) then added. The mixture was left in the cold for 24 hours and acidified. The precipitated *ethyl* α-2 : 4-*dinitrophenyl*-γ-*phenylacetoacetate* (19 g.) crystallised from alcohol in thick yellow needles, m. p. 127° (Found: C, 58·2; H, 4·5; N, 7·5. $C_{18}H_{16}O_7N_2$ requires C, 58·1; H, 4·3; N, 7·5%). In acetone it gave a red coloration with ferric chloride.

3-*Hydroxy*-1-*ethoxy*-2-2′ : 4′-*dinitrophenylnaphthalene*, prepared by boiling the preceding ester with the equivalent amount of sodium ethoxide for 4 hours, crystallised from alcohol in long, yellow, silky needles, m. p. 179° (Found: C, 61·1; H, 4·1; N, 7·9. $C_{18}H_{14}O_6N_2$ requires C, 61·0; H, 3·95; N, 7·9%). The *acetyl* derivative (acetic anhydride–sulphuric acid method) crystallised from benzene–alcohol in long, yellow, silky needles, m. p. 191—192° (Found: C, 60·1; H, 4·1; N, 7·3. $C_{20}H_{16}O_7N_2$ requires C, 60·6; H, 4·0; N, 7·1%).

1 : 3-*Dihydroxy*-2-2′ : 4′-*dinitrophenylnaphthalene*, obtained by boiling the above acetoacetate for 30 minutes, or the preceding naphthalene derivative for 5 minutes, with 5% aqueous sodium hydroxide and acidifying the solution, had m. p. 279° after crystallisation from benzene–alcohol (Found: C, 59·0; H, 3·2; N, 8·6. $C_{16}H_{10}O_6N_2$ requires C, 58·9; H, 3·1; N, 8·6%).

α-*Chloro*-α-*benzylethylene and* β-*Chloro*-α-*phenyl*-Δ$^{\alpha}$-*propylene*.—Benzyl methyl ketone (67 g.) and phosphorus pentachloride (110 g.) in dry benzene (300 c.c.) were boiled for 4 hours, the benzene and phosphoryl chloride removed under reduced pressure, ice added, and the mixture left overnight in the ice-chest. The chloro-olefins were extracted with ether and washed successively with dilute pyridine, dilute hydrochloric acid, and sodium bicarbonate solution (yield, 80 g.). Fractional distillation gave: (1) 35 g., b. p. 105—107°/26 mm. (Found: C, 70·9; H, 6·1; Cl, 23·1. C_9H_9Cl requires C, 70·8; H, 5·9; Cl, 23·3%); (2) 20 g., b. p. 120—124°/26 mm. (Found: C, 70·9; H, 6·0; Cl, 22·8%); (3) 6 g., above 124°.

Ozonisation of fraction (1), *immediately* after distillation, in chloroform containing alcohol gave ethyl phenylacetate (detected and estimated by hydrolysis to the acid), denoting that (1) consisted entirely of α-*chloro*-α-*benzylethylene*. When the same fraction was ozonised a few days later, benzoic acid was detected in the products, the amount of ethyl phenylacetate being correspondingly decreased. Fraction (2) gave the same ozonisation products as those obtained in the second ozonisation of (1). When redistilled many days after their first fractionation, fractions (1) and (2) were found to have attained the same composition—that of an equilibrium mixture of the two chloro-olefins. One can safely say, therefore, that fraction (1) is α-chloro-α-benzylethylene and fraction (2) is β-chloro-α-phenyl-Δ$^{\alpha}$-propylene (cf. Farmer and Hose, J., 1933, 965) and that these exist in the ratio 35 : 20 in the equilibrium mixture. Boiling the equilibrium mixture with concentrated alcoholic sodium ethoxide for 24 hours failed to eliminate all the chlorine.

α-*Chloro*-α-*benzyl*-Δ$^{\alpha}$-*propylene and* β-*Chloro*-α-*phenyl*-Δ$^{\alpha}$-*butylene*.—Benzyl ethyl ketone (74 g.) was treated with phosphorus pentachloride exactly as in the case of benzyl methyl ketone. After the washing, the product gave (1) 42 g., b. p. 114—116°/23 mm. (Found: Cl, 21·1%); (2) 19 g., b. p. 123—125°/23 mm. (Found: Cl, 20·9. $C_{10}H_{11}Cl$ requires Cl, 21·3%); (3) 7 g., above 130°.

In course of time fraction (1), α-*chloro*-α-*benzyl*-Δ$^{\alpha}$-*propylene*, and fraction (2), β-*chloro*-α-*phenyl*-Δ$^{\alpha}$-*butylene*, changed into the same equilibrium mixture, about 70% of the products of ozonisation of which consisted of ethyl phenylacetate.

α-*Chloro*-α-*benzyl*-Δ$^{\alpha}$-*butylene and* β-*Chloro*-α-*phenyl*-Δ$^{\alpha}$-*amylene*.—The product obtained in the same way from benzyl propyl ketone (81 g.) gave on distillation (1) α-*chloro*-α-*benzyl*-Δ$^{\alpha}$-*butylene* (46 g.), b. p. 134—135°/22 mm. (Found: Cl, 19·2%); (2) β-*chloro*-α-*phenyl*-Δ$^{\alpha}$-*amylene* (22 g.), b. p. 145—147°/22 mm. (Found: Cl, 19·2. $C_{11}H_{13}Cl$ requires Cl, 19·7%); (3) 7 g., above 150°.

Fractions (1) and (2) ultimately changed into the same equilibrium mixture, about 70% of the products of ozonisation of which consisted of ethyl phenylacetate.

α-*Chloro*-α-p-*nitrobenzylethylene and* β-*Chloro*-α-p-*nitrophenyl*-Δ$^{\alpha}$-*propylene*.—*p*-Nitrobenzyl methyl ketone (35·8 g.) and phosphorus pentachloride (45 g.) in dry benzene (120 c.c.) were refluxed for 4 hours. After the usual treatment and washing, the chloro-olefins were obtained as a liquid containing 10% of a solid, m. p. 78° after crystallisation from light petroleum (b. p. 60—70°) (Found: C, 54·6; H, 4·0; N, 6·7; Cl, 18·1. $C_9H_8O_2NCl$ requires C, 54·7; H, 4·1; N, 7·1; Cl, 18·0%); 70% of the product was a liquid, b. p. 161—162°/11 mm. or 134—136°/3 mm. (Found: C, 54·5; H, 4·1; N, 7·0; Cl, 18·4%); the remaining 20% was a high-boiling liquid.

Ozonisation of the solid proved it to be *β-chloro-α-p-nitrophenyl-Δ$^{\alpha}$-propylene*. Ozonisation of the liquid *immediately* after distillation gave mostly ethyl *p*-nitrophenylacetate, m. p. and mixed m. p. 65°, thus proving it to be *α-chloro-α-p-nitrobenzylethylene*. When the liquid was ozonised a few days after distillation, *p*-nitrobenzaldehyde, m. p. 106°, and *p*-nitrobenzoic acid, m. p. 238°, were obtained in amounts approximating to 23% of the products. Attempts to precipitate a solid from this liquid failed. This was taken to indicate that 23% of the equilibrium mixture is not the solid, m. p. 78°, but its liquid geometrical isomer. Crystals, m. p. 78°, were, however, formed in the liquid after about 1 year.

Action of dilute alkali solution. The solid did not give a coloration with aqueous or alcoholic alkali. The liquid equilibrium mixture gave a dark violet coloration with very dilute alkali solution. An ethereal solution of the liquid was washed with 5% sodium hydroxide solution until the washings ceased to be red. The ethereal solution, after cooling, deposited the solid, m. p. 78°.

Action of sodium ethoxide. The solid was boiled for 1 hour with alcoholic sodium ethoxide, and the mixture diluted, acidified, and shaken with ether, which extracted yellow *β-ethoxy-α-p-nitrophenyl-Δ$^{\alpha}$-propylene*, m. p. 96° after crystallisation from light petroleum (b. p. 60—70°) (Found: C, 63·6; H, 6·3; N, 6·7. $C_{11}H_{13}O_3N$ requires C, 63·7; H, 6·3; N, 6·8%). When the boiling was prolonged to 4 hours, this substance was again produced together with *α-p-nitrophenylallylene*, which crystallised from light petroleum (b. p. 60—70°) in long prisms, m. p. 108° (Found: C, 67·1; H, 4·4; N, 8·6. $C_9H_7O_2N$ requires C, 67·1; H, 4·4; N, 8·7%). The liquid equilibrium mixture also was treated with alcoholic sodium ethoxide; the solution became dark violet. After 1 hour's boiling, the above ether and the acetylenic compound were isolated, but more than half of the product was an unidentified brown-red solid insoluble in ether.

α-Chloro-α-2 : 4-dinitrobenzylethylene and β-Chloro-α-2 : 4-dinitrophenyl-Δ$^{\alpha}$-propylene.—2 : 4-Dinitrobenzyl methyl ketone (22·4 g.) and phosphorus pentachloride (22·5 g.) in dry benzene (60 c.c.) were refluxed for 4 hours and the chloro-olefins were isolated after the usual treatment and washing. *β-Chloro-α-2 : 4-dinitrophenyl-Δ$^{\alpha}$-propylene*, which crystallised from dilute alcohol in straw-coloured needles, m. p. 91—93° (Found: C, 44·2; H, 3·0; N, 11·4; Cl, 14·7. $C_9H_7O_4N_2Cl$ requires C, 44·5; H, 2·9; N, 11·5; Cl, 14·6%), formed 10% of the product; its constitution was shown by ozonolysis. The rest was a heavy liquid, which was ozonised in chloroform containing alcohol; about one-fourth of the products of ozonisation was 2 : 4-dinitrobenzaldehyde, m. p. 71—72°, and 2 : 4-dinitrobenzoic acid, m. p. 183°. The solid product gave no colour with alcoholic sodium ethoxide, but sodium chloride was precipitated in the cold. After dilution ether extracted *α-2 : 4-dinitrophenylallylene*, which crystallised from light petroleum (b. p. 60—70°) in small yellowish lumps, m. p. 77° (Found: C, 52·0; H, 3·0; N, 13·2. $C_9H_6O_4N_2$ requires C, 52·4; H, 2·9; N, 13·6%). No ether was formed. The crude liquid chloro-olefin gave a dark violet coloration with sodium ethoxide and a dark brown-red solid insoluble in ether (not investigated) was obtained.

FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, October 7th*, 1942.]

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23. *Melanthigenin and its Identity with Hederagenin.*

By (MISS) ZAHIRA MUSTAFA and GABRA SOLIMAN.

Melanthigenin, the acidic sapogenin obtainable by hydrolysis of an alcoholic extract of the defatted seeds of *Nigella sativa* L. (Ranunculaceæ), is shown to have the formula $C_{30}H_{48}O_4$ and to be identical with hederagenin.

THE seeds of *Nigella sativa* L. were first examined by Greenish (*Pharm. J.*, 1880, **10**, 909, 1013), who found that the alcoholic extract contained, apart from a small quantity of resin, a saponin, which was precipitated on dilution with water and after purification melted at 205°; it was named melanthic acid, $C_{30}H_{33}O_7$. Greenish hydrolysed melanthic acid with hydrochloric acid to melanthigenin, to which he assigned the formula $C_{14}H_{22}O_2$ without giving a description of its chemical properties. Kobert and Kruskal (*Arb. Pharmacol. Inst. Dorpat*, 1891, **6**, 29) and Kobert and Schulz (*ibid.*, 1896, **14**, 37, 112; see Abderhalden, "Biochemisches Handlexicon," 1912, VII, 205) gave the formulæ $C_{30}H_{52}O_{10}$ and $C_{29}H_{50}O_{10}$, respectively, to melanthic acid.

Greenish found that the saponin content of the seeds was variable, amounting to 1% and 0·1% in seeds of Russian and German origin, respectively. The seeds of Egyptian origin examined in the present work contained no water-insoluble saponin. The alcoholic extract gave no precipitate on dilution with water. When the alcohol was completely removed, a brownish water-soluble syrup was obtained, which on hydrolysis with hydrochloric acid in presence of alcohol gave a dark brownish, crystalline precipitate of melanthigenin. After purification through its sodium salt melanthigenin crystallised from dilute pyridine in white prisms, m. p. above 325°, which gave the general colour reactions of sapogenin acids.

Analysis indicated that melanthigenin has the formula $C_{30}H_{48}O_4$ and contains a free carboxyl group as indicated by titration with standard alkali. The presence of two hydroxyl groups was indicated by the formation of a diacetate, m. p. 170°, and a dibenzoate. Further, the acid was converted into its methyl ester by the action of methyl sulphate, and the ester converted into its diacetate and dibenzoate. The formulæ, melting points, and properties of these derivatives are in agreement with those of hederagenin (Jacobs, *J. Biol. Chem.*, 1925, **63**, 621; Winterstein and Meyer, *Z. physiol. Chem.*, 1931, **199**, 37; Kitasato and Sone, *Acta Phytochim.*, 1932, **6**, 179). Only the methyl ester was not obtained directly pure, but on treatment with hydrochloric acid in presence of dry acetone, it was converted into the acetonyl derivative, which was hydrolysed to the pure ester, m. p. 237—238° (Jacobs, *loc. cit.*, p. 631). These derivatives were shown to be identical with authentic specimens prepared from hederagenin isolated from the leaves of *Hedera helix* (Van der Haar, *Biochem. Z.*, 1916, **76**, 342). The sapogenin was shown to contain one double bond by titration with standard perbenzoic acid, and its position with respect to the carboxyl group was indicated by the formation of a diformyl-lactone. This was deformylated, and the free lactone converted into its diacetate (cf. Winterstein and Meyer, *loc. cit.*; Winterstein and Wiegand, *Z. physiol. Chem.*, 1931, **199**, 46).

EXPERIMENTAL.

Isolation of the Sapogenin.—The crushed seeds of *Nigella sativa* L. were extracted three times with light petroleum (b. p. 60—80°), dried, finely ground, and extracted with hot light petroleum, which removed the last trace of fatty matter (loss in weight, about 30%). The defatted meal (1 kg.) was refluxed with alcohol for 6 hours, and the liquid filtered while luke warm; this process was repeated twice and the combined filtrates were evaporated under diminished pressure on the water-bath. The brownish syrup obtained was dissolved in water, a trace of fatty matter removed by extraction with light petroleum, and the dark aqueous solution triturated with freshly precipitated lead hydroxide (100 g.), kept overnight, and filtered. Lead was removed from the limpid yellow filtrate by hydrogen sulphide, and the excess of the gas expelled under reduced pressure on the water-bath. The solution containing the saponin was mixed with alcohol and hydrochloric acid so that it contained about 40% of alcohol and 10% of hydrogen chloride; when it was heated on the water-bath for 2 hours, a whitish gelatinous precipitate separated, which gradually changed into a dark brownish, crystalline mass.

The crude sapogenin (13·5 g.) was dissolved in a mixture of alcohol (200 c.c.) and 10% sodium hydroxide solution (200 c.c.), refluxed (animal charcoal) for 2 hours, and filtered while hot. The filtrate was gradually diluted with sodium hydroxide solution until a permanent white precipitate began to separate; it was then cooled, and the white plates of the sodium salt collected. A solution of the salt in alcohol was heated with animal charcoal, and the hot filtrate acidified with acetic acid. Instantly the solution was transformed into a gelatinous mass, which gradually changed into a microcrystalline precipitate (10 g.). This crystallised from dilute pyridine in white prisms, m. p. above 325°, not depressed by hederagenin [Found: C, 76·3, 76·2; H, 10·2, 10·1; CO_2H (by titration), 9·6, 9·6; *M*, 467·2, 463·1. Calc. for $C_{29}H_{47}O_2(CO_2H)$: C, 76·2; H, 10·2; CO_2H, 9·5%; *M*, 472·4].

O-Acyl Derivatives.—A solution of the sapogenin (1 g.) in pyridine (10 c.c.) and acetic anhydride (10 c.c.) was heated for an hour. The product, isolated in the usual manner, crystallised from dilute methanol in needles, m. p. 170°, identical with hederagenin diacetate [Found: C, 73·3; H, 9·3. Calc. for $C_{29}H_{45}O_2(CH_3{\cdot}CO)_2(CO_2H)$: C, 73·3; H, 9·4%].

A solution of the sapogenin (1 g.) in pyridine (20 c.c.) was heated with benzoyl chloride (2 c.c.) for an hour at 90° and poured into cold water. The resinous product, after being washed with water acidified with sulphuric acid, was heated with a small volume of methanol; the insoluble portion crystallised from alcohol in platelets, m. p. 292°, identical with hederagenin dibenzoate (Found: C, 77·4; H, 8·0. Calc. for $C_{44}H_{58}O_6$: C, 77·6; H, 8·3%).

The Methyl Ester.—Methyl sulphate (8 c.c.) was gradually added to a solution of the sapogenin (3 g.) in alcohol (30 c.c.) and 10% sodium hydroxide solution (30 c.c.); after addition of more alkali and methyl sulphate, the ester was collected. It crystallised from methanol in needles, m. p. 228°, identical with an authentic specimen. The m. p. was gradually raised by successive crystallisations, yet the pure ester was directly obtained by hydrolysis of its acetonyl derivative prepared by the action of a few drops of hydrochloric acid on a solution of the impure ester in dry acetone. The acetonyl derivative crystallised from absolute alcohol in platelets, m. p. 250° (cf. Jacobs, *loc. cit.*) (Found: C, 77·3; H, 10·3. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·3%). An analytical specimen of the ester was prepared when the acetonyl derivative was hydrolysed by heating with hydrochloric acid in alcohol for 20 minutes. It crystallised from methanol in needles, m. p. 237—238° (Found: C, 76·6; H, 10·2. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·4%).

O-Acyl Derivatives of the Ester.—The methyl ester reacted with acetic anhydride in pyridine to give the diacetyl derivative, which crystallised from methanol in needles, m. p. 192°, identical with an authentic specimen (Found: C, 73·7; H, 9·5. Calc. for $C_{35}H_{54}O_6$: C, 73·6; H, 9·5%).

The dibenzoate was prepared by heating a solution of the ester (1 g.) in pyridine with benzoyl chloride (2 c.c.) for 20 hours at 40°. The mixture was poured into water, and the resinous product washed and crystallised from methanol and alcohol; it formed plates, m. p. 195—197° (Found: C, 77·9; H, 8·2. Calc. for $C_{45}H_{58}O_6$: C, 77·8; H, 8·4%).

The Unsaturated Centre.—The diacetate of the methyl ester was titrated with a standard solution of perbenzoic acid (Levy and Lagrave, *Bull. Soc. chim.*, 1925, **37**, 1598) and the values found were 1·01 and 1·0 atom of oxygen, indicating the presence of one double bond.

The position of the double bond with respect to the carboxyl group became obvious from the formation of a diformyllactone when the sapogenin (1 g.) was refluxed with anhydrous formic acid (30 c.c.) for 7 hours. After dilution with water, the product was isolated; it crystallised from methyl alcohol–ethyl alcohol in needles, m. p. 265° (Found: C, 72·6; H, 9·0. Calc. for $C_{32}H_{48}O_6$: C, 72·7; H, 9·2%). It was deformylated by heating with 5% alcoholic potassium hydroxide for 45 minutes; the alcohol was then removed by distillation, and the residue extracted with chloroform after dilution with water. The neutral chloroform solution left on evaporation a white residue, which crystallised from chloroform–alcohol in plates, m. p. above 350° (Found: C, 76·5; H, 10·4. Calc. for $C_{30}H_{48}O_4$: C, 76·2; H, 10·2%). Acetylation of the free lactone with acetic anhydride in presence of pyridine gave a diacetyl-lactone, which crystallised from methanol in plates, m. p. 251° (Found: C, 73·5; H, 9·4. Calc. for $C_{34}H_{52}O_6$: C, 73·3; H, 9·4%). None of these lactones was hydrolysed by treatment with alakli.

Melting points are not corrected, analyses are by Dr. Weiler, and the specimens were dehydrated in a high vacuum before analysis.

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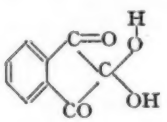
24. *Studies on Indene Derivatives. Part II. Triketohydrindene.*

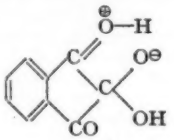
By ALEXANDER SCHÖNBERG and RADWAN MOUBACHER.

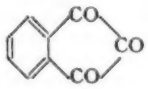
Triketohydrindene has been prepared by the action of thionyl chloride on triketohydrindene hydrate (ninhydrin). An inner-salt formula (II) for ninhydrin is advanced and some new reactions are mentioned.

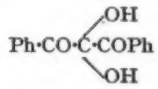
TRIKETOHYDRINDENE (III) has not hitherto been described. It can be prepared by heating its hydrate (I) (ninhydrin) with thionyl chloride (yield, quantitative) or in a vacuum, but is obtained pure with difficulty by the latter method. When the hydrate is heated in the presence of oxygen, phthalic anhydride is formed. Triketohydrindene forms dark red needles, which melt to a bluish-green liquid; on cooling, the red crystals are re-formed. The colour of solutions of triketohydrindene depends on the solvent. When the blue-green solution of triketohydrindene in benzene is shaken with water, decoloration occurs almost instantly, owing to the formation of the colourless hydrate (I). This hydrate is readily soluble in cold water, whereas the hydrate

of diphenyl triketone (IV) is only very sparingly soluble. In order to explain the ready solubility of ninhydrin in water and its remarkable thermal stability we allocate to it the inner-salt formula (II). The possibility of resonance between the structures (I) and (II) should be stressed.


(I.)


(II.)


(III.)


(IV.)

Experimental.

Preparation of Triketohydrindene.—(1) *By the action of thionyl chloride on ninhydrin.* Freshly distilled thionyl chloride (50 c.c.) was heated for about 40 minutes with ninhydrin (0·5 g.) recently crystallised from water. The reaction vessel was connected by means of a ground glass joint to a condenser fitted with a receiver connected to a filter-pump. The apparatus was exhausted, and the vessel heated in a bath at 60—70°. The ninhydrin dissolved, forming a solution having the colour of malachite-green; as the solution became more concentrated (owing to evaporation of the thionyl chloride), reddish-violet crystals of triketohydrindene separated. After about 45 minutes, all the thionyl chloride had distilled off and the vessel was placed in a vacuum desiccator containing sodium hydroxide in order to remove the last traces of thionyl chloride. The triketohydrindene (yield, quantitative) melted at 255°, forming a green liquid (Found : C, 67·7; H, 2·5. Calc. for $C_9H_4O_3$: C, 67·5; H, 2·5%).

(2) *By the thermal decomposition of ninhydrin.* Ninhydrin was heated in a vacuum in a bath at about 190°. It turned red and a sublimate was formed consisting of red needles and colourless material. The red crystals were separated by hand and washed with benzene; they melted at 255°, forming a green liquid, and were identical with the crystals obtained in (1).

Physical Properties of Triketohydrindene.—Triketohydrindene sublimes in a vacuum, forming violet-red crystals. It dissolves readily in benzonitrile, forming a violet-red solution, but only with difficulty in cold acetic anhydride, hot benzene, and nitrobenzene at 100°, bluish-green solutions being formed. It is practically insoluble in carbon tetrachloride and light petroleum (b. p. 50—60°). The solution of triketohydrindene in glacial acetic acid is blue-green when hot and practically colourless when cold, probably owing to the formation of a dissociable addition compound of acetic acid with the second carbonyl group of triketohydrindene. Triketohydrindene dissolves in concentrated sulphuric acid, forming a violet solution. Fused triketohydrindene (glass, quartz, or platinum vessel) has a very intense green colour. This occurs even when the substance is heated in a vacuum, showing that the production of the green colour is not due to atmospheric oxidation.

Action of Water on Triketohydrindene.—Triketohydrindene was heated for about 1 minute with a small quantity of water in the absence of direct sunlight. When the hot solution was filtered, evaporated somewhat, and allowed to cool, colourless crystals of ninhydrin, m. p. 139°, undepressed by an authentic specimen, separated in practically quantitative yield (Found : C, 60·2; H, 3·5. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·3%).

Physical and Chemical Properties of Ninhydrin.—When ninhydrin is heated in benzene, a bluish-green solution is gradually produced owing to the formation of triketohydrindene. A colourless aqueous solution of ninhydrin, freshly prepared from a pure sample and protected from light, does not liberate iodine from aqueous potassium iodide, even after acidification. The colourless crystals of ninhydrin turn reddish when exposed to sunlight. Where these crystals are treated with hot water, and aqueous potassium iodide added to the filtrate, iodine is liberated after acidification.

Action of Oxygen on Ninhydrin.—Ninhydrin was heated in a vessel at 190° (bath temperature) in a current of oxygen. A sublimate of phthalic anhydride was obtained; after purification this had m. p. 129°, undepressed by an authentic specimen. The fluorescein test for phthalic anhydride was positive.

Fouad I University, Cairo. [*Received, December 28th*, 1942.]

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25. *Qualitative Semimicro-analysis with Reference to Noyes and Bray's System : The Aluminium Group.*

By Christina C. Miller.

A scheme of analysis for the metals composing the aluminium group of Noyes and Bray's system is presented for the detection and approximate estimation of 0·25—50 mg. of aluminium, chromium, or zinc, and 0·25—10 mg. of beryllium, tungsten, uranium, or vanadium, in mixtures containing phosphate and a maximum of 50 mg. referred to the metals. In separate portions of the solution zinc is precipitated as zinc (copper) mercury thiocyanate; beryllium, tungsten, and vanadium are detected, respectively, by means of morin, toluene-3 : 4-dithiol, and tannin; chromium (VI), after its separation from vanadium and tungsten, is tested for with diphenylcarbazide; and, finally, aluminium and zinc are separated from the bulk of the other metals. Aluminium is precipitated as cæsium alum, and uranium, after further separations, as uranyl ferrocyanide.

Semimicro-analytical methods have already been applied by Miller and Lowe (J., 1940, 1258, 1263) and Miller (J., 1941, 72, 786) to six groups of Noyes and Bray's system (" A System of Qualitative Analysis for the Rare Elements," 1927). This paper describes their extension to the aluminium group. Benedetti-Pichler and Spikes (*Mikrochem.*, Molisch-Festschrift, 1936, 3, 36) have analysed the group on the micro-scale, and Fischer, Dietz, Brünger, and Grieneisen (*Angew. Chem.*, 1936, **49**, 719) on a scale only a little smaller than Noyes and Bray's.

In Noyes and Bray's scheme the solution remaining after removal of the copper and the tellurium group is successively treated with ammonium acetate and ferric nitrate, and ammonium hydroxide and hydrogen sulphide, whereby two groups of metals are precipitated. When the acid solutions of these are treated with

sodium hydroxide and sodium peroxide, two alkaline extracts result, which are combined to form the aluminium group. It contains aluminium, beryllium, chromium, tungsten, uranium, vanadium, zinc, and phosphate, with perhaps a little contaminating titanium, and iron and gallium, if these have not been satisfactorily eliminated earlier. Phosphate is not tested for, but its influence on other tests must be known. Provision has therefore been made for the detection and estimation of the above seven metals, in mixtures containing phosphate, within the limits set forth in the summary.

The scheme presented differs considerably from those cited. For instance, beryllium, tungsten, vanadium, zinc, and chromium are tested for in separate portions of the group solution, the first four in a very direct manner. The importance of the toluene-3 : 4-dithiol test for tungsten (Hamence, *Analyst*, 1940, **65**, 152) is stressed. Benedetti-Pichler and Spikes stated that they " could not recommend any chemical method for the detection of *small* quantities of tungsten in the presence of large quantities of chromium, uranium, vanadium and phosphate ion." This test admirably fulfils the purpose (see Note 2).

Experimental.

Preparation of the Group for Analysis.—Mixtures containing the chlorides of aluminium, beryllium, uranium, and zinc, and sodium or potassium chromate, tungstate, vanadate, and phosphate were treated in Pyrex tubes with 0·6 g. of sodium peroxide and a little sodium hydroxide to ensure complete solution. They were heated to decompose the excess of peroxide and analysed according to the following tabulated scheme.

Aluminium Group.

(The figures in parentheses are referred to in " Notes on Methods and Tests.")

Solution.—Contains sodium aluminate, beryllate, chromate, tungstate, peruranate, vanadate, zincate, and phosphate, with traces of peroxide. Make a definite volume, *e.g.*, 10 ml., and test separate portions as follows.:

(*a*) Test 0·05—0·2% for Be. Boil with 0·05 ml. of 2N-HCl and a few mg. of $NaHSO_3$. Add 1 ml. of 2N-NaOH, remove any precipitate that forms, then dilute with 5 ml. of water and add 0·1 ml. of morin (0·02% in acetone). A green fluorescence shows **Be.** Compare with standards. (1).

(*b*) Test 0·1—1% for W. Acidify with HCl, add a little $NaHSO_3$, and evaporate to dryness in a test-tube. To the residue add 0·5 ml. of 11N-HCl, 0·5 ml. of *n*-butyl acetate, and solid toluene-3 : 4-dithiol. Heat at 70° for 10—15 mins., add a little more dithiol, and dilute with 0·5 ml. of water. If the ester layer is coloured blue-green, showing **W,** compare with standards. (2).

(*c*) Test 0·1—1% for V. Add one drop of 0·05M-KH_2PO_4, a few mg. of $NaHSO_3$, 0·2 ml. of 10% aqueous tartaric acid, and water to make 1 ml., followed by 0·05 ml. of 10% aqueous tannin and solid sodium acetate in large excess. A blue colour attaining its maximum intensity in a few mins. shows **V.** If a white precipitate (Al) or a brown colour (U) appears add 0·05 ml. of 20% aqueous NH_4F and compare at once with standards. (3).

(*d*) Test 10% for Zn. Add a few mg. of $NaHSO_3$, acidify with HNO_3, evaporate to dryness, and dissolve the residue in 0·5 ml. of N-HNO_3. To the solution add 0·05 ml. of 20% aqueous NH_4F, 0·05 ml. of 0·01M-$CuSO_4$, and 0·2 ml. of ammonium mercury thiocyanate reagent (30 g. of $HgCl_2$ and 33 g. of NH_4SCN in 100 ml. of water). Shake briskly. A violet or black precipitate shows **Zn.** If the colour of the precipitate is unsatisfactory (V present) dissolve it in a drop of concentrated HNO_3, dilute with water, and add ammonium mercury thiocyanate. Compare with standards. (4).

(*e*) Test 0·1—1% for Cr. Add a few mg. of $NaHSO_3$, acidify with 2N-H_2SO_4, and expel SO_2. Add one drop of 0·1M-$FeCl_3$, and an excess of 2N-NaOH. Boil and separate $Fe(OH)_3$, $Cr(OH)_3$, and perhaps $Na_2U_2O_7$. Dissolve the precipitate in 0·05 ml. of 2N-H_2SO_4, add 0·05 ml. of saturated aqueous Br_2, and gradually make alkaline with 0·5N-NaOH. Set aside for several mins. in order to form Cr^{VI}, then heat gently, add a few mg. of phenol to destroy excess Br_2, and separate and reject the precipitate of $Fe(OH)_3$ and perhaps $Na_2U_2O_7$. Acidify the centrifugate with 2N-H_2SO_4 making about 1 ml. of solution 0·2—0·3N in acid. Add diphenylcarbazide (0·25% in 50% aqueous acetone) until an excess is present. A pink or red colour shows **Cr.** If tribromophenol has separated centrifuge it down or extract it with chloroform. Compare with standards prepared directly from chromate. (5).

(*f*) Test 10% for Al and U. Pass CO_2 into the hot solution, diluted to 1·5 ml. After 5 mins., cool the solution and continue the passage of CO_2 for 15 mins. Centrifuge and wash the precipitate with 0·5M-$NaHCO_3$. (6).

Precipitate. $Al(OH)_3$, $BeCO_3$ (part), $ZnCO_3$. Dissolve in $>0·1$ ml. of 4N-H_2SO_4, add solid Cs_2SO_4 and stir thoroughly. A white crystalline precipitate of cæsium alum shows **Al,** which is compared with standards. To confirm a small precipitate, separate and wash it, dissolve it in a minimum amount of N-HCl, and test with alizarin or morin. (7).

Solution. Na_2CrO_4, Na_3VO_4, Na_2WO_4, Be (part) and U as complex carbonates. Gradually acidify with 5N-HCl and evaporate to dryness. Dissolve the residue in 0·2 ml. of 11N-HCl and 0·6 ml. of water. Add an excess of 10% aqueous cupferron and extract the brown V complex and the excess of the reagent with three 1 ml. portions of chloroform. To the aqueous layer add 0·4 g. of KSCN and extract twice with 0·5 ml. of *iso*amyl acetate, rejecting the ester layers. Finally extract uranium thiocyanate with 2 ml. of ethyl acetate. Evaporate the ester layer to dryness (steam-bath), dissolve the residue in 0·1—0·3 ml. of 0·5N-HCl, add 0·05—0·15 ml. of 0·25M-$K_4Fe(CN)_6$, and stir thoroughly. A dark brown precipitate shows **U.** Compare with standards prepared from U that has been extracted by means of ethyl acetate from 0·5 ml. of N-HCl containing 0·1 g. of NaCl and 0·2 g. of KSCN. (8).

Notes on Methods and Tests.—The experimental technique was the same as formerly.

Note 1. The method prescribed for this excellent test is based on that developed for quantitative purposes by Sandell (*Ind. Eng. Chem. Anal.*, 1940, **12**, 674, 762). The conditions under which the aluminium group is isolated are such that possible interfering metals, *e.g.*, scandium and calcium, are adequately removed. Chromium (VI) and traces of peroxide, which prevented the fluorescence, had to be reduced with sodium bisulphite. For the present purpose the interference of zinc was negligible. In the estimation of beryllium the solutions were examined in vials (1 in. diameter) held against a dark background under a daylight lamp. The amount of beryllium must not exceed 5 μg.; 0·25 μg. was easily detected.

Note 2. This method of applying the toluene-3 : 4-dithiol test for tungsten (Miller, J., 1941, 792) permitted the detection of <1 μg. in a mixture containing at least 5 mg. of each of the group components, including phosphate. Sodium

bisulphite was added to reduce chromium(VI) and vanadium(V), which would otherwise have used up much of the expensive reagent.

Note 3. The production of a blue colour or precipitate, when sodium acetate was added to a slightly acid solution containing vanadium and tannin, was seriously hindered by tungstate, and might be masked by an excess of aluminium or uranium. Oxidising agents had to be absent. The presence of not less than an equal weight of phosphate (PO_4''') and an excess of tartaric acid counteracted the influence of tungstate, and the addition of fluoride dissolved the tannin complex of aluminium and almost eliminated the colour due to uranium. A 100-fold excess of tungsten halved the sensitivity of the test. Chromium(III) in excess modified the colour but did not prevent the detection of the minimum amount of vanadium under consideration. Of possible group contaminants iron and titanium did not prevent the detection of the same amount of vanadium, and gallium behaved like aluminium. 1 μG. of vanadium was detectable, and for estimations 10 μg. was the upper limit.

Note 4. The precipitation of zinc as white zinc mercury thiocyanate permitted its detection in minimum amount in solutions containing maximum amounts of all the other group components except vanadium which decomposed the reagent. Chromium(III) was preferable to chromium(VI). Cuvelier and Bosch (*Natuurwetensch. Tijds.*, 1936, **18**, 9; through A., 1936, 560) have shown that the test should preferably be made in nitrate solution. In the presence of copper, which alone gives a green precipitate, the precipitates from more than twice the weight of zinc are coloured violet, and from an equal weight, black. Consequently, if a constant amount of copper were always added one could utilise the colour of the precipitate to estimate small quantities of zinc. It was then advisable to mask with ammonium fluoride a possible trace of iron that otherwise behaved like copper. The double precipitation effectively eliminated the interference of an excess of vanadium.

Note 5. This test for chromium(VI) (Feigl, "Qualitative Analyse mit Hilfe von Tüpfelreaktionen," 1938, 230; Sandell, *Ind. Eng. Chem. Anal.*, 1936, **8**, 336), which is applicable in the presence of many metals, had to be done in the absence of vanadate and tungstate which gave a brown and a turbid solution, respectively. The method prescribed for the separation and oxidation of chromium(III) is based on Järvinen's observations (*Z. anal. Chem.*, 1928, **75**, 1).

Note 6. In order to separate aluminium, beryllium, and zinc from the other group components, Noyes and Bray (*op. cit.*, p. 176) neutralised the solution with nitric acid and then added about 1% of sodium bicarbonate, which small amount ensured complete precipitation of beryllium and usually held uranium in solution. Sometimes, however, uranyl vanadate entered the precipitate, and a small amount of uranium was carried down by a large precipitate. The modified process prescribed was utilised solely in order to separate aluminium from phosphotungstate, and uranium from zinc (see Notes 7 and 8). Since it was immaterial whether or not beryllium was precipitated, and greater dilution of the original solution and a higher concentration of sodium bicarbonate favoured the retention of uranium in the solution, the strongly alkaline mixture was made 50% more dilute than usual, and a final concentration of 10% of sodium bicarbonate was assured by saturating it with carbon dioxide. In this way 25 μg. of uranium were adequately separated from a mixture containing 5 mg. of precipitable metals, and 25 μg. of aluminium from a mixture containing 5 mg. of non-precipitable metals and 5 mg. of phosphate (PO_4''').

Note 7. Provided that the metals were present mainly as sulphates in a small volume of dilute sulphuric acid, 25 μg. of aluminium were detectable in the presence of the maximum excesses of zinc, uranium and beryllium under consideration. At least 25-fold excesses of chromium(VI) and vanadium(V) were permissible, but phosphotungstate had to be absent, since its cæsium salt is insoluble. The test with morin or alizarin (Feigl, *op. cit.*, pp. 244, 246) served to distinguish it from cæsium alum. Gallium which behaves like aluminium must be effectively removed before testing for the latter, and preferably before isolating the aluminium group for analysis (see Noyes and Bray, *op. cit.*, p. 151).

Note 8. The test for uranium with potassium ferrocyanide is very distinctive, but it must be made in the absence of other metals that give insoluble ferrocyanides, *e.g.*, vanadium and zinc, and group contaminants such as titanium, iron, and gallium. The concentration of the uranium salt must not be too low. In the bicarbonate treatment zinc, titanium, iron, and part of the gallium were eliminated. The cupferron–chloroform treatment removed all but a minor amount of vanadium, even in the presence of tungstate, and any titanium, iron, or gallium accidentally present. It was found that a small amount of vanadium in association with phosphotungstate gave very slowly with potassium ferrocyanide a brown solution from which a precipitate resembling uranyl ferrocyanide eventually deposited. The addition of an excess of potassium thiocyanate to the solution (~2N in hydrochloric acid) and extraction with *iso*amyl acetate prevented this interference by removing the tungstate without loss of uranium. The uranium thiocyanate left in the aqueous layer was then readily extracted by means of ethyl acetate, the removal of which permitted the precipitation of uranyl ferrocyanide under the conditions of acidity found most suitable by Noyes and Bray (*op. cit.*, p. 421). As a small amount might coagulate very slowly, it was advisable to re-examine a doubtful test after ½ hour.

Analysis of Mixtures.—As a final check five mixures of unknown composition were analysed. Each mixture contained 25 mg. of phosphate (PO_4'''). The results shown in the table, which are considered satisfactory, are the estimated weights (in mg.) of the metals found. Where these differed from the actual amounts taken, the latter are shown in parentheses.

Element.	Al.	Be.	Cr.	W.	U.	V.	Zn.
No. 1	0·25	0	0·2 (0·25)	7 (5)	0	6 (7)	10 (12)
2	0·5	3 (4)	0	2	0·25	0·6 (1)	20 (30)
3	10 (12)	1·5 (2)	30 (24)	6 (7)	2	0·15 (0·25)	0·25
4	0	13 (10)	0·5 (1)	0	5 (8)	0	3 (2)
5	20 (25)	0·15 (0·25)	4 (5)	0·25	0·5	7 (10)	0

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26. *Gallium. Part VI. The Separation of Gallium and Germanium from Alkaline Extracts of Germanite by Electrolysis.*

By D. J. LLOYD and W. PUGH.

Direct electrolysis of the alkaline extract of germanite yields a mixed deposit of gallium and germanium metals which is easily separated, yielding pure gallium and germanium tetrachloride. Yields of over 80% are recovered directly in this manner, the remainder being recovered from the spent electrolyte and from the cathodic gases. This method of extraction is considerably simpler and more efficient than any previously described.

THE advantages of alkali digestion as a means of separating both gallium and germanium from the greater bulk of copper and iron sulphides in germanite ore have already been reported by Sebba and Pugh (J., 1937, 1371), who have also described a chemical method of isolating pure gallium and germanium dioxide from the alkali extract. The chief advantages of the method are comparative simplicity and high yields: the yields of both metals in actual extractions were considerably higher than had ever been reported in the mineral. Subsequently (J., 1937, 1373), the same authors described the conditions for the successful electrodeposition of pure gallium from alkaline solutions. The latter work immediately suggested the possibility of the direct separation of gallium by electrolysis of the alkali extract of the mineral. This would have the merit of great simplification because, in the chemical method already referred to, the major part of the work is concerned with the removal of impurities before the gallium is electrolysed out.

Though it has not been found possible to isolate gallium alone in this way, it is possible to obtain a mixed deposit of gallium and germanium metals from which pure gallium and germanium tetrachloride or dioxide can easily be obtained. The deposit is entirely free from arsenic, and this simple process of electrolysis, therefore, separates completely one of the most troublesome elements associated with gallium and germanium. The only impurities are traces of molybdenum, antimony, and lead.

However, as shown by Sebba and Pugh (*loc. cit.*), it is not possible to recover gallium completely by electrolysis of alkaline solutions; and Schwartz, Heinrich, and Hollstein (*Z. anorg. Chem.*, 1936, **229**, 159) have shown that the same applies to germanium. Under the conditions to be described, it is shown that recoveries of the order of 80—85% of both metals are possible. The remainder may be recovered by chemical means, or the spent electrolyte may be used for the extraction of a fresh portion of the mineral. If the chemical method is adopted, the presence of arsenic in the liquor does not complicate the separation of gallium because the arsenic is in the reduced condition.

During electrolysis a small proportion of the germanium is volatilised as hydride, and this may be recovered by decomposition in a heated tube.

EXPERIMENTAL.

Extraction of Gallium and Germanium.—The separation of the two metals from 1 kg. of ore was carried out by the method already described by Sebba and Pugh (*loc. cit.*); the main alkaline filtrate (1½—2 l.) was electrolysed directly, after removal of any crystals of sodium trioxysulpharsenate which separated. (The original washings were not added to the main filtrate but used for the extraction of a second portion of ore.)

Choice of Electrodes.—Platinum was not very satisfactory as a cathode, chiefly because of the difficulty of removing the deposit, which adhered strongly, and because chlorination was subsequently found to be the best means of dealing with the mixed deposit. Copper and nickel were both satisfactory. The deposit adhered well and was easily removed afterwards by bending, whereupon it cracked and flaked off. Hall and Koenig (*Trans. Electrochem. Soc.*, 1934, **65**, 215) have described the use of copper for the electrodeposition of germanium from alkaline solution. Tin was found to be useless because it became too brittle after a few hours' use.

As anode, platinum was certainly the best, but nickel was also satisfactory. Nickel anodes suffered a loss of approximately 0·2% in weight after 100 hours' use. Nickel was never found in the cathodic deposit.

Temperature.—Hall and Koenig (*loc. cit.*) recommended temperatures of 70—80° for the electrodeposition of germanium from alkaline solutions, but we found temperatures of this order quite unsuitable because the deposit was loose and non-adherent, and some gallium melted off and dropped back into the bath, where it redissolved. At 25—35° the deposit was hard and adherent. No external heating was necessary to maintain these temperatures.

Current Density.—In most of the experimental work, the cathode was a sheet of copper 6 cm. long and 5 cm. wide. The nickel anode was about twice this size. The cell carried a current of 1—1·5 amps. at 3—4 volts, giving a C.D. at the cathode of 0·016—0·025 amp./cm.^{2}, depending on the concentration of the electrolyte. In the actual extraction method worked out, the electrodes were about four times the above sizes, and electrolysis was carried out at 12—15 volts with a current of 4—5 amps.

Effect of Concentration.—Varying the concentration of alkali in the electrolyte had little or no effect either on the rate of deposition or on the nature of the deposit. Good results were obtained from solutions that were 6N with respect to sodium hydroxide, and this was approximately the concentration of the alkali extract of the ore. The factor which determined the rate of deposition, the efficiency of recovery, and the physical nature of the deposit was the concentration of gallium and germanium. The ratio of the concentration of these two metals in the ore and in the alkali extract was approximately 1 : 5.

Deposition of the metals became very slow when the concentration of gallium fell to 0·5 g./l.; on the other hand, when its concentration exceeded 5 g./l., although the rate of deposition was high, the initial deposit was soft and silvery and formed a poor base for further deposition. Gallium was deposited preferentially, for the deposit formed during the first few hours was generally soft and silvery in appearance, with evidence of globules of gallium, but as deposition proceeded, it became black, hard, and adherent. Analysis showed that the ratio Ga : Ge in the deposit formed during the first 3 hours was much higher than it was in the electrolyte.

The change in the rate of deposition of the mixed metal with time was a curious one. For the first 10 hours, when gallium was actively depositing, the rate was proportional to the concentration of the metals in solution; thereafter the rate fell off rapidly. This would indicate that the deposition voltage of germanium on gallium is lower than it is on germanium. Hall and Koenig (*loc. cit.*) reported that the deposition of germanium on copper ceases when the copper is coated with germanium and thereafter only hydrogen is evolved.

It was not possible to remove all the gallium and germanium by electrolysis under any conditions investigated, for the rate of deposition of germanium became so low after a certain point that loss of germanium as hydride was serious; on prolonged electrolysis, the cathode diminished in weight. The practical limit for successful deposition was reached when the concentrations of gallium and germanium had been reduced to 0·5 and 3 g./l., respectively, irrespective of the concentration of alkali in the solution.

In order to attain reasonable efficiency, therefore, it was necessary to employ solutions of relatively high concentration; but, as already noted, concentrations of gallium exceeding 5 g./l. gave unsatisfactory deposits. In practice, from 2 l. of extract containing 10 g. of gallium and 50 g. of germanium (from 1 kg. of ore) it was possible to obtain within 36—48 hours a satisfactory deposit of mixed metal consisting of 9 g. of gallium and 41 g. of germanium, representing over 80% recovery of both metals.

Recovery of Metals from Spent Electrolyte.—The spent electrolyte was most usefully employed for the extraction of a fresh portion of ore and this was repeated for a third portion. At this stage it became necessary to recover the metals by chemical means. Gallium was completely precipitated as hydroxide by neutralisation (pH 5), and germanium as dioxide by making the filtrate strongly ammoniacal. The precipitates were then added to a fresh alkali extract for electrolysis.

Treatment of Electrolytic Deposit.—The deposit dissolved only with difficulty. When finely powdered, it was readily attacked by hot concentrated nitric acid and by hot sulphuric acid, but in both cases, the action soon ceased because of deposition of a white coating of germanium dioxide on the metal surface. The effect of *aqua regia* was no better. Alternate treatment with acid and alkali eventually dissolved the metals. The best means of attack was chlorination. The coarsely powdered metal was placed in a hard-glass tube and heated in a current of chlorine, the vapours being condensed in a small distilling flask well cooled in a freezing mixture. A white residue of gallium oxide usually remained in the tube unless both the metal powder and the chlorine were thoroughly dried. This residue was washed into the receiver with a small quantity of concentrated hydrochloric acid. The distillate was then fractionated, germanium tetrachloride passing over at 78—80°. It was purified and treated by methods described by Dennis and Hance (*J. Amer. Chem. Soc.*, 1922, **44**, 304). The gallium chloride solution remaining was purified from traces of molybdenum, antimony, and lead by treatment with hydrogen sulphide in acid and in alkaline solution, and the gallium was finally recovered by electrolysis of alkaline solution as described by Sebba and Pugh (*loc. cit.*).

Recovery of Germanium volatilised as Hydride.—During the later stages of the electrolysis, when hydrogen evolution was considerable, there was much loss of germanium as hydride at the cathode, about 8—10% of it being thus lost. It was recovered by enclosing the cathode within a glass " bell " and leading the gases through a glass tube maintained at 350—400° in a tubular furnace (Muller and Smith, *ibid.*, p. 1909). Although this was effective in recovering every trace of germanium, the modification necessarily caused a considerable increase in the resistance of the cell and consequently a decrease in the rate of deposition. The black deposit was a mixture of germanium and arsenic. It was chlorinated and fractionally distilled in a current of chlorine. The details of the separation of germanium and arsenic have been adequately described (Dennis and Papish, *ibid.*, 1921, **43**, 2131).

UNIVERSITY OF CAPE TOWN. [*Received, December 14th*, 1942.]

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27. *Gallium. Part VII. Gallium Perchlorate Hydrates and a Gallium Perchlorate–Urea Complex.*

By D. J. LLOYD and W. PUGH.

Gallium is shown to conform with the other members of its group in forming hydrated and highly soluble perchlorates; a *nonahydrate* and a hexahydrate are described. The former loses $3H_2O$ readily, but the remaining $6H_2O$ are strongly co-ordinated, and attempts to dehydrate the hexahydrate lead to decomposition of the perchlorate. A 6-co-ordination *compound* of gallium perchlorate and urea is also described.

THE congeners of gallium are all known to form crystalline perchlorates. No less than four hydrates of aluminium perchlorate are described, containing 15, 12, 9, and $6H_2O$ (Gmelin's " Handbuch," 8th Edn., No. 35, Part B, p. 217); one hydrate of indium perchlorate, the octahydrate (Mathers and Schleuderberg, *J. Amer. Chem. Soc.*, 1908, **30**, 212), and one of thallic perchlorate, the hexahydrate (Gewecke, *Z. anorg. Chem.*, 1912, **75**, 272), are described. No anhydrous perchlorates of these metals have yet been prepared.

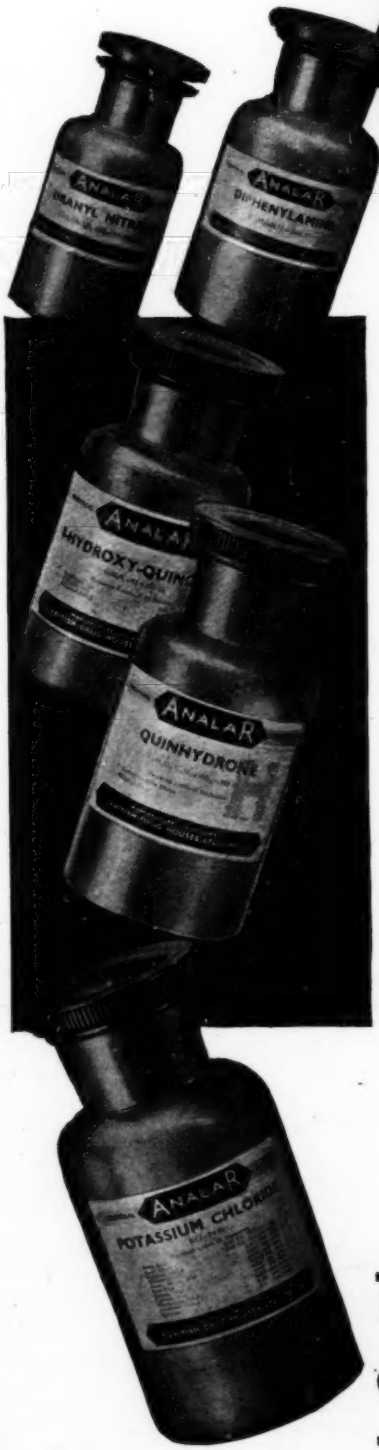
Of gallium perchlorate nothing was known when the present work was commenced. Willard and Fogg (*J. Amer. Chem. Soc.*, 1937, **59**, 1197) had used solutions of gallium hydroxide in perchloric acid for the electrodeposition of gallium and, while the present work was in progress, Foster (*ibid.*, 1939, **61**, 3123) described the preparation of two hydrates containing 6 and $9\frac{1}{2}H_2O$. We had already prepared the hexahydrate and a *nonahydrate*, but we have been unable to confirm the existence of Foster's second hydrate: we are of the opinion that this was identical with our nonahydrate and that his methods of analysis were not precise enough to distinguish between the two formulæ. The differences in composition would be very small, especially as regards gallium, and it is our experience that the method, used by Foster, of estimating perchlorate as the potassium salt from alcoholic solution is not precise enough for the purpose. We have, in fact, been able to confirm our results by a determination of chloride ion after decomposition of the perchlorate. We have also shown that both hydrates decompose on strong heating to gallium oxide and that the yield of oxide is quantitative in both cases, the volatile products consisting mainly of water vapour, chlorine, and oxygen.

Determinations of loss in weight with time at different temperatures have shown that the nonahydrate is converted into the hexahydrate below 100° and into basic perchlorates of indefinite composition above 100°. At 125° the product obtained approximated closely in composition to $3Ga_2O_3,Ga(ClO_4)_3$. There was no evidence of the formation of any lower hydrates or of the anhydrous salt.

Urea and other weak organic bases form co-ordination compounds with many inorganic salts; $Al(ClO_4)_3,6CO(NH_2)_2$ has been described by Barbieri (*Atti R. Accad. Lincei*, 1915, **24**, 917). Gallium perchlorate is now shown to form a similar *compound* with urea, but all attempts to prepare co-ordination compounds with pyridine and thiourea by similar means failed. In the former case, pyridine perchlorate always separated, and in the latter case thiourea crystallised unchanged.

EXPERIMENTAL.

Gallium Perchlorate Nonahydrate.—Gallium metal (5 g.) was dissolved in concentrated nitric acid as described by Sebba and Pugh (J., 1937, 1376), and the solution evaporated nearly to dryness to remove the excess of acid. A small excess of 60% perchlorate acid was added, and evaporation continued until the syrupy liquid solidified on cooling. Water was then added, and the evaporation repeated in order to remove all traces of nitric acid. The crystalline mass



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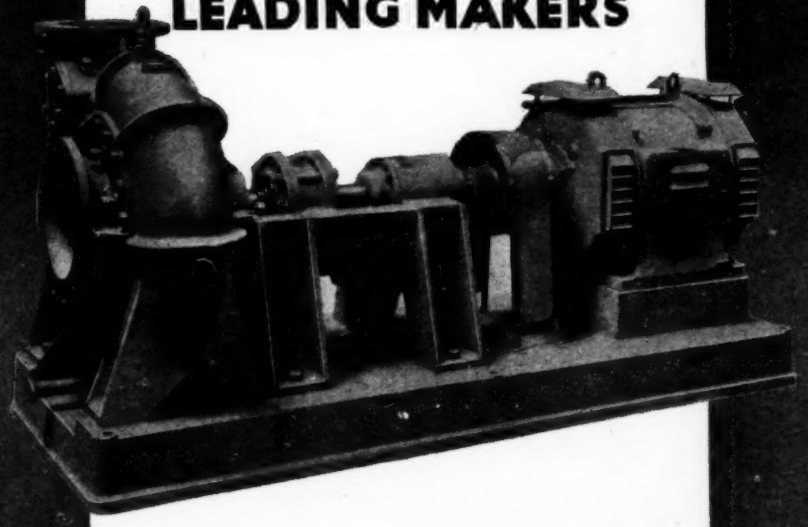

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